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8 9	Attorneys for Defendants FibroGen, Inc., Enrique Conterno, James Schoen Mark Eisner, and Pat Cotroneo	neck,
10	UNITED STATES	DISTRICT COURT
11	NORTHERN DISTRI	CT OF CALIFORNIA
12		
13	IN RE FIBROGEN, INC., SECURITIES	Case No. 3:21-cv-02623-EMC
14	LITIGATION	CLASS ACTION
15		DECLARATION OF ALEXANDER J. KASNER IN SUPPORT OF DEFENDANTS' MOTION TO
16		DISMISS PLAINTIFFS' CONSOLIDATED CLASS ACTION COMPLAINT AND REQUEST
17 18		FOR JUDICIAL NOTICE AND CONSIDERATION OF DOCUMENTS INCORPORATED BY REFERENCE
19		Hearing Date: April 28, 2022
20		Time: 1:30 pm Courtroom: 5
21		Judge: Hon. Edward M. Chen
22		
23	I, Alexander J. Kasner, hereby declare as	follows:
24	1. I am an associate at the law firm C	ooley LLP, counsel for defendants FibroGen, Inc.
25	("FibroGen" or the "Company"), Enrique Con	terno, James Schoeneck, Mark Eisner, and Pat
26	Cotroneo (collectively, "Defendants") in the abo	ove-captioned litigation. I am a member in good
27	standing of the Bar of California. I submit this	declaration in support of Defendants' Motion to

Dismiss Plaintiffs' Consolidated Class Action Complaint ("Motion") as well as Defendants'

COOLEY LLP ATTORNEYS AT LAW PALO ALTO

DECL. OF ALEXANDER J. KASNER ISO MOTION TO DISMISS CAC 3:21-cv-02623-EMC concurrently filed Request for Judicial Notice and Consideration of Documents Incorporated by Reference.¹ I have personal knowledge of the facts set forth in this Declaration, and if called to testify, I could and would testify competently thereto.

- 2. This Declaration covers two topics. In Part I of this Declaration, I describe the documents that Defendants ask this Court to consider incorporated by reference into the CAC or of which to take judicial notice. Where applicable, I note where the documents are cited in the CAC. Those documents are attached as Exhibits to this Declaration. In Part II of this Declaration, I describe the steps I took to analyze stock sales by the Individual Defendants and non-defendant Thomas Neff, using public filings with the Securities and Exchange Commission ("SEC").
- I. DOCUMENTS SUBJECT TO DEFENDANTS' REQUEST FOR JUDICIAL NOTICE AND INCORPORATION BY REFERENCE
- 3. **Exhibit A** attached hereto are relevant excerpts of a true and correct copy of FibroGen's Annual Report for the year ending December 31, 2017, on Form 10-K, filed with the SEC on February 27, 2018. The Form 10-K is publicly available on the SEC's website at https://www.sec.gov/Archives/edgar/data/0000921299/000156459018003508/fgen-10k 20171231.htm. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 4. **Exhibit B** attached hereto is a true and correct copy of a Statistical Analysis Plan for roxadustat Study 608 dated August 2, 2018, entitled *A Phase 3 Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of Roxadustat for the Treatment of Anemia in Chronic Kidney Disease Patients not on Dialysis authored by Astellas Pharma Europe B.V. This document is attached as it appeared on ClinicalTrials.gov, a website maintained by the National Library of Medicine (an institute within the National Institutes of Health), and is publicly available at*
- https://clinicaltrials.gov/ct2/show/NCT01887600?term=roxadustat&u_sap=Yes&draw=2&rank=
- 2. Relevant portions of the Exhibit are highlighted for the Court's convenience.
 - 5. **Exhibit** C attached hereto is a true and correct copy of a Statistical Analysis Plan

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DECL. OF ALEXANDER J. KASNER ISO MOTION TO DISMISS CAC 3:21-cv-02623-EMC

¹ References to "CAC ¶" are to paragraphs of Plaintiffs' Consolidated Class Action Complaint. Otherwise, any reference to "paragraph" or "subparagraph" are internal cross-references to portions of this Declaration.

for roxadustat Study 002 dated September 28, 2018, entitled A Phase 3 Randomized, Open-Label
Active-Controlled Study of the Safety and Efficacy of Roxadustat in the Treatment of Anemia in
Dialysis Patients authored by AstraZeneca. This document is attached as it appeared or
ClinicalTrials.gov, a website maintained by the National Library of Medicine, and is publicly
available

https://clinicaltrials.gov/ct2/show/NCT02174731?term=roxadustat&u_sap=Yes&draw=2&rank=

8. Relevant portions of the Exhibit are highlighted for the Court's convenience.

- 6. **Exhibit D** attached hereto is a true and correct copy of a Statistical Analysis Plan for roxadustat Study 063 dated October 14, 2018, entitled *A Phase 3 Multicenter, Randomized, Open-Label, Active-Controlled Study of the Efficacy and Safety of Roxadustat in the Treatment of <i>Anemia in Incident Dialysis Patients* authored by FibroGen. This document is attached as it appeared on ClinicalTrials.gov, a website maintained by the National Library of Medicine, and is publicly available at https://clinicaltrials.gov/ct2/show/study/NCT02052310?term=roxadustat&u_sap=Yes&draw=2&r ank=3. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 7. **Exhibit E** attached hereto is a true and correct copy of a press release issued by FibroGen on December 20, 2018, entitled *FibroGen Announces Positive Topline Results from Three Global Phase 3 Trials of Roxadustat for Treatment of Anemia in Patients with Chronic Kidney Disease.* The press release is publicly available on FibroGen's website at https://investor.fibrogen.com/news-releases/news-release-details/fibrogen-announces-positive-topline-results-three-global-phase-3. This document is referenced in the CAC at ¶ 51 and ¶¶ 142-44. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 8. **Exhibit F** attached hereto is a true and correct copy of a press release issued by AstraZeneca plc on December 20, 2018, entitled *AstraZeneca Announces Phase III OLYMPUS and ROCKIES trials for Roxadustat met their primary endpoints in CKD patients with anaemia*. The press release is publicly available on AstraZeneca's website at https://www.astrazeneca.com/media-centre/press-releases/2018/phase-iii-olympus-and-rockies-trials-for-roxadustat-met-their-primary-endpoints-in-chronic-kidney-disease-patients-with-

https://www.sec.gov/Archives/edgar/data/921299/000156459019018022/fgen-

10q_20190331.htm. This document is referenced in the CAC at ¶ 37 and ¶ 162. Relevant portions of the Exhibit are highlighted for the Court's convenience.

- 15. **Exhibit M** attached hereto is a true and correct copy of a transcript of FibroGen's presentation at the 40th Annual Goldman Sachs Global Healthcare Conference on June 12, 2019, published by S&P Global Market Intelligence and referenced in the CAC at ¶ 57 and ¶¶ 163-66. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 16. **Exhibit N** attached hereto is a true and correct copy of a transcript of FibroGen's Earnings Call for the second quarter of 2019 on August 8, 2019, published by S&P Global Market Intelligence. This document is referenced in the CAC at ¶¶ 59, ¶¶ 167-68, and ¶ 170. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 17. **Exhibit O** attached hereto are relevant excerpts of a true and correct copy of FibroGen's Quarterly Report for the quarter ending June 30, 2019, on Form 10-Q, filed with the SEC on August 8, 2019. The Form 10-Q is publicly available on the SEC's website at https://www.sec.gov/ix?doc=/Archives/edgar/data/921299/000156459019030812/fgen-
- 10q_20190630.htm. This document is referenced in the CAC at ¶¶ 169-170. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 18. **Exhibit P** attached hereto is a true and correct copy of a press release issued by FibroGen on November 8, 2019, entitled *FibroGen Announces Positive Phase 3 Pooled Roxadustat Safety and Efficacy Results for Treatment of Anemia in Chronic Kidney Disease*. The press release is publicly available on FibroGen's website at https://investor.fibrogen.com/news-releases/news-release-details/fibrogen-announces-positive-phase-3-pooled-roxadustat-safety-and. This document is referenced in the CAC at ¶¶ 61-63 and ¶¶ 171-75. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 19. **Exhibit Q** attached hereto is a true and correct copy of a press release issued by AstraZeneca on November 8, 2019, entitled *AstraZeneca Announces Roxadustat Phase III* programme pooled analyses showed positive efficacy and no increased cardiovascular risk in patients with anaemia from chronic kidney disease. The press release is publicly available on

AstraZeneca's website at https://www.astrazeneca.com/media-centre/press-releases/2019/roxadustat-phase-iii-programme-pooled-analyses-showed-positive-efficacy-and-no-increased-cv-risk-in-patients-with-anaemia-from-chronic-kidney-disease.html#!. Relevant portions of the Exhibit are highlighted for the Court's convenience.

- 20. **Exhibit R** attached hereto is a true and correct copy of a transcript of FibroGen's Earnings Call for the third quarter of 2019 on November 11, 2019, published by S&P Global Market Intelligence. This document is referenced in the CAC at ¶ 22, ¶ 64, ¶¶ 177-78, and ¶ 248. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 21. **Exhibit S** attached hereto are relevant excerpts of a true and correct copy of FibroGen's Quarterly Report for the quarter ending September 30, 2019, on Form 10-Q, filed with the SEC on November 12, 2019. The Form 10-Q is publicly available on the SEC's website at https://www.sec.gov/Archives/edgar/data/0000921299/000156459019042615/fgen-10q_20190930.htm. This document is referenced in the CAC at ¶ 22 and ¶¶ 181-83. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 22. **Exhibit T** attached hereto is a true and correct copy of a blog post entitled *Victory Lap Re-up: What's harder to find, the PYRENEES data set in an FGEN presentation, or an Andorra on a map?*, published by BuyersStrike!, a blogging website with investment recommendations that purports to be authored by a short seller, on November 14, 2019 and publicly available at: https://buyersstrike.com/2019/11/. This document is referenced in the CAC at ¶ 179 and ¶¶ 182-83. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 23. **Exhibit U** attached hereto is a true and correct copy of a transcript of FibroGen's presentation at the 9th Annual SVB Leerink Global Healthcare Conference on February 25, 2020, published by S&P Global Market Intelligence and referenced in the CAC at ¶ 67 and ¶¶ 184-86. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 24. **Exhibit V** attached hereto is a true and correct copy of a transcript of FibroGen's Earnings Call for the fourth quarter of 2019 on March 2, 2020, published by S&P Global Market Intelligence. This document is referenced in the CAC at ¶¶ 187-88. Relevant portions of the Exhibit are highlighted for the Court's convenience.

- 25. **Exhibit W** attached hereto are relevant excerpts of a true and correct copy of FibroGen's Annual Report for the year ending December 31, 2019, on Form 10-K, filed with the SEC on March 2, 2020. The Form 10-Q is publicly available on the SEC's website at https://www.sec.gov/Archives/edgar/data/0000921299/000156459020008161/fgen-
- 10k_20191231.htm. This document is referenced in the CAC at ¶¶ 187-88. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 26. **Exhibit X** attached hereto is a true and correct copy of a transcript of FibroGen's Earnings Call for the first quarter of 2020 on May 7, 2020, published by S&P Global Market Intelligence. This document is referenced in the CAC at ¶ 189 and ¶ 191. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 27. **Exhibit Y** attached hereto is a true and correct copy of a transcript of FibroGen's presentation at the Bank of America Securities 2020 HealthCare Conference on May 14, 2020, published by S&P Global Market Intelligence and referenced in the CAC at ¶ 68 and ¶¶ 190-91. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 28. **Exhibit Z** attached hereto is a true and correct copy of a transcript of FibroGen's presentation at the Jefferies Healthcare Conference on June 2, 2020, published by Thomson Reuters and referenced in the CAC at ¶ 192 and ¶ 194. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 29. **Exhibit AA** attached hereto is a true and correct copy of a transcript of FibroGen's 2020 Annual Meeting of Shareholders on June 4, 2020, published by S&P Global Market Intelligence. This document is referenced in the CAC at ¶¶ 193-94. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 30. **Exhibit BB** attached hereto is a true and correct copy of a transcript of FibroGen's presentation at the Goldman Sachs 41st Annual Global Healthcare Conference on June 9, 2020, published by S&P Global Market Intelligence and referenced in the CAC at ¶ 5, ¶ 68, and ¶¶ 195-97. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 31. **Exhibit CC** attached hereto is a true and correct copy of a transcript of FibroGen's Earnings Call for the second quarter of 2020 on August 6, 2020, published by S&P Global Market

Intelligence. This document is referenced in the CAC at ¶ 198 and ¶ 200. Relevant portions of the Exhibit are highlighted for the Court's convenience.

- 32. **Exhibit DD** attached hereto are relevant excerpts of a true and correct copy of FibroGen's Quarterly Report for the quarter ending June 30, 2020, on Form 10-Q, filed with the SEC on August 6, 2020. The Form 10-Q is publicly available on the SEC's website at https://www.sec.gov/Archives/edgar/data/0000921299/000156459020037760/fgen-10q_20200630.htm. This document is referenced in the CAC at ¶ 20 and ¶¶ 199-200. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 33. **Exhibit EE** attached hereto is a true and correct copy of a transcript of FibroGen's presentation at the Citi 15th Annual Biopharma Virtual Conference on September 9, 2020, published by S&P Global Market Intelligence and referenced in the CAC at ¶ 69, ¶ 201, and ¶¶ 203-04. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 34. **Exhibit FF** attached hereto is a true and correct copy of a transcript of FibroGen's presentation at the Morgan Stanley 18th Annual Global Healthcare Conference on September 16, 2020, published by S&P Global Market Intelligence and referenced in the CAC at ¶¶ 202-04. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 35. **Exhibit GG** attached hereto is a true and correct copy of a transcript of FibroGen's Earnings Call for the third quarter of 2020 on November 5, 2020, published by S&P Global Market Intelligence. This document is referenced in the CAC at ¶¶ 205-06. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 36. **Exhibit HH** attached hereto is a true and correct copy of a transcript of FibroGen's presentation at the Stifel Virtual Healthcare Conference on November 17, 2020, that I understand was provided to FibroGen by Stifel and referenced in the CAC at ¶ 207 and ¶ 209. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 37. **Exhibit II** attached hereto is a true and correct copy of a transcript of FibroGen's presentation at the Jefferies 2020 Virtual London Healthcare Conference on November 19, 2020, published by S&P Global Market Intelligence and referenced in the CAC at ¶ 5, ¶ 69, and ¶¶ 208-09. Relevant portions of the Exhibit are highlighted for the Court's convenience.

- 38. **Exhibit JJ** attached hereto is a true and correct copy of a press release issued by FibroGen on December 1, 2020, entitled *FibroGen Announces Retirement of K. Peony Yu, M.D., and Appointment of Mark Eisner, M.D., M.P.H. as Chief Medical Officer*. The press release is publicly available on FibroGen's website at https://investor.fibrogen.com/news-releases/news-release-details/fibrogen-announces-retirement-k-peony-yu-md-and-appointment-mark. This document is referenced in the CAC at ¶ 23, ¶ 72, and ¶ 258. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- Frost, Senior Vice President, Regulatory Affairs and Medical Writing, of FibroGen, regarding a Citizen Petition by Epstein Becker & Green Regarding the Pending New Drug Application for Roxadustat, dated December 9, 2020. This document was published on December 10, 2020 and purports to be a Comment responding to a Citizen Petition from Epstein, Becker and Green, P.C. This document, and the Citizen Petition, are published on Regulations.gov, a website managed by the General Services Administration's eRulemaking Program for public participation in Federal rules and regulations, and is publicly available at https://www.regulations.gov/comment/FDA-2020-P-2193-0006. This document is referenced in the CAC at ¶¶ 211-15 and ¶ 248. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 40. **Exhibit LL** attached hereto is a true and correct copy of a press release issued by FibroGen on March 1, 2021, entitled *FibroGen Provides Regulatory Update on Roxadustat*. The press release is publicly available on FibroGen's website at https://investor.fibrogen.com/news-releases/news-release-details/fibrogen-provides-regulatory-update-roxadustat-0. This document is referenced in the CAC at ¶ 8, ¶¶ 74, ¶¶ 216-17, and ¶ 264. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 41. **Exhibit MM** attached hereto is a true and correct copy of a transcript of FibroGen's Earnings Call for the fourth quarter of 2020 on March 1, 2021, published by S&P Global Market Intelligence. This document is referenced in the CAC at ¶ 76 and ¶ 218. Relevant portions of the Exhibit are highlighted for the Court's convenience.
 - 42. **Exhibit NN** attached hereto are relevant excerpts of a true and correct copy of

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FibroGen's Annual Report for the year ending December 31, 2020, on Form 10-K, filed with the SEC on March 1, 2021. The Form 10-K is publicly available on the SEC's website at https://www.sec.gov/Archives/edgar/data/0000921299/000156459021009871/fgen-

- 10k_20201231.htm. This document is reference in the CAC at ¶ 38, ¶¶ 43-44, and ¶ 256. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 43. **Exhibit OO** attached hereto is a true and correct copy of a transcript of FibroGen's presentation at the Cowen 41st Annual Health Care Conference on March 2, 2021, published by S&P Global Market Intelligence and referenced in the CAC at ¶¶ 219-20. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 44. **Exhibit PP** attached hereto is a true and correct copy of a press release issued by FibroGen on April 6, 2021, entitled *FibroGen Provides Additional Information on Roxadustat*. The press release is publicly available on FibroGen's website at https://investor.fibrogen.com/news-releases/news-release-details/fibrogen-provides-additional-information-roxadustat. This document is referenced in the CAC at ¶ 222 and ¶¶ 227-29 (*see also passim*). Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 45. **Exhibit QQ** attached hereto is a true and correct copy of a transcript of FibroGen's Special Call on April 6, 2021, published by S&P Global Market Intelligence. This document is referenced in the CAC at ¶¶ 223-29. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 46. **Exhibit RR** attached hereto is a true and correct copy of a transcript of FibroGen's Earnings Call for the first quarter of 2021 on May 10, 2021, published by S&P Global Market Intelligence. This document is referenced in the CAC at ¶ 230 and ¶ 232. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 47. **Exhibit SS** attached hereto is a true and correct copy of a transcript of FibroGen's presentation at the Bank of America Securities 2021 Virtual Health Care Conference on May 13, 2021, published by S&P Global Market Intelligence and referenced in the CAC at ¶¶ 231-32. Relevant portions of the Exhibit are highlighted for the Court's convenience.
 - 48. **Exhibit TT** attached hereto is a true and correct copy of a transcript of FibroGen's

presentation at the Jefferies 2021 Virtual Healthcare Conference on June 4, 2021, published by S&P Global Market Intelligence and referenced in the CAC at ¶ 233 and ¶ 235. Relevant portions of the Exhibit are highlighted for the Court's convenience.

- 49. **Exhibit UU** attached hereto is a true and correct copy of a transcript of FibroGen's presentation at the Goldman Sachs 42nd Annual Global Healthcare Conference on June 10, 2021, published by S&P Global Market Intelligence and referenced in the CAC at ¶¶ 234-35. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 50. **Exhibit VV** attached hereto is a true and correct copy of an FDA Advisory Committee Briefing document titled *FDA Briefing Information for the July 15, 2021 Meeting of the Cardiovascular and Renal Drugs Advisory Committee*, published on July 13, 2021. This document is attached as it appeared on the FDA's website and is publicly available at https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-time-information-july-15-2021-meeting-cardiovascular-and-renal-drugs-advisory-committee. This document is referenced in the CAC at ¶¶ 103-04 and 228. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 51. **Exhibit WW** attached hereto is a true and correct copy of a FibroGen Advisory Committee Briefing document titled *FibroGen Briefing Information for the July 15, 2021 Meeting of the Cardiovascular and Renal Drugs Advisory Committee*. This document is attached as it appeared on the FDA's website and is publicly available at https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-time-information-july-15-2021-meeting-cardiovascular-and-renal-drugs-advisory-committee. The Briefing document was used in conjunction with the FDA Advisory Committee referenced in the CAC, including but not limited to ¶¶ 103-09. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 52. **Exhibit XX** attached hereto is a true and correct copy of a transcript of the FDA Advisory Committee Meeting titled *Transcript for the July 15, 2021 Meeting of the Cardiovascular and Renal Drugs Advisory Committee*. This document is published on the FDA's website and is publicly available at https://www.fda.gov/advisory-committee-calendar/updated-time-information-july-15-2021-meeting-cardiovascular-and-renal-drugs-

1	advisory-committee. This document is referenced in the CAC at ¶¶ 105-106 and ¶¶ 108-09.									
2	Relevant portions of the Exhibit are highlighted for the Court's convenience.									
3	53. Exhibit YY attached hereto is a true and correct copy of FibroGen's Quarterly									
4	Report for the quarter ending June 30, 2021, on Form 10-Q, filed with the SEC on August 9, 2021.									
5	The Form 10-Q is publicly available on the SEC's website at									
6	https://www.sec.gov/Archives/edgar/data/0000921299/000156459021042639/fgen-									
7	10q_20210630.htm. This document is referenced in the CAC at ¶ 256. Relevant portions of the									
8	Exhibit are highlighted for the Court's convenience.									
9	54. Exhibit ZZ attached hereto is a true and correct copy of a press release issued by									
10	Astellas Pharma Inc. on August 20, 2020, entitled Astellas Receives European Commission									
11	Approval for First-in-Class EVRENZO (roxadustat) for Adult Patients with Symptomatic Anemia									
12	of Chronic Kidney Disease. The press release is publicly available on Astellas's website at									
13	https://www.astellas.com/us/news/5966. Relevant portions of the Exhibit are highlighted for the									
14	Court's convenience.									
15	55. Exhibit AAA attached hereto are true and correct copies of Form 4s reporting									
16	Changes in Beneficial Ownership filed by or on behalf of Dr. K. Peony Yu, with the SEC between									
17	May 20, 2016 and December 17, 2020, to the extent those Form 4s reflect the sale and/or disposition									
18	of stock (for the reasons discussed below in Part II). Those Forms 4s are available at									
19	https://www.sec.gov/edgar/search/#/dateRange=custom&category=form-									
20	cat2&ciks=0001621328&entityName=Yu%2520K%2520Peony%2520(CIK%25200001621328)									
21	&startdt=2016-02-09&enddt=2020-12-17. Relevant portions of the Exhibit are highlighted for the									
22	Court's convenience.									
23	56. Exhibit BBB attached hereto are true and correct copies of Form 4s reporting									
24	Changes in Beneficial Ownership filed by or on behalf of Enrique Conterno, with the SEC between									
25	May 20, 2016 and July 15, 2021, to the extent those Form 4s reflect the sale and/or disposition of									
26	stock (for the reasons discussed below in Part II), or the purchase of stock on the open market.									
27	Those Forms 4s are available at									
28	https://www.sec.gov/edgar/search/#/q=FibroGen&dateRange=custom&category=form-									

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cat2&ciks=0001476151&entityName=Conterno%2520Enrique%2520A%2520(CIK%252000014 76151)&startdt=2020-01-07&enddt=2022-01-07. Relevant portions of the Exhibit are highlighted for the Court's convenience.

- 57. **Exhibit CCC** attached hereto are true and correct copies of Form 4s reporting Changes in Beneficial Ownership filed by or on behalf of Pat Cotroneo, with the SEC between May 20, 2016 and July 15, 2021, to the extent those Form 4s reflect the sale and/or disposition of stock (for the reasons discussed below in Part II). Those Forms 4s are available at https://www.sec.gov/edgar/search/#/q=FibroGen&dateRange=custom&category=formcat2&ciks=0001621334&entityName=Cotroneo%2520Pat%2520(CIK%25200001621334)&start dt=2016-01-22&enddt=2021-09-09. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 58. **Exhibit DDD** attached hereto are true and correct copies of Form 4s reporting Changes in Beneficial Ownership filed by or on behalf of James Schoeneck, with the SEC between May 20, 2016 and July 15, 2021, to the extent those Form 4s reflect the sale and/or disposition of stock (for the reasons discussed below in Part II). Those Forms 4s are available at https://www.sec.gov/edgar/search/#/q=FibroGen&dateRange=custom&category=formcat2&ciks=0001420987&entityName=Schoeneck%2520James%2520A%2520(CIK%252000014 20987)&startdt=2016-06-10&enddt=2021-05-28. Relevant portions of the Exhibit are highlighted for the Court's convenience.
- 59. Exhibit EEE attached hereto are true and correct copies of Form 4s reporting Changes in Beneficial Ownership filed by or on behalf of Thomas Neff, with the SEC between May 20, 2016 and August 23, 2019, to the extent those Form 4s reflect the sale and/or disposition of stock (for the reasons discussed below in Part II). Those Forms 4s are available at https://www.sec.gov/edgar/search/#/q=FibroGen&dateRange=custom&category=formcat2&ciks=0001623238&entityName=Neff%2520Thomas%2520B%2520(CIK%2520000162323 8)&startdt=2016-01-13&enddt=2019-08-22. Relevant portions of the Exhibit are highlighted for the Court's convenience.

II. ANALYSIS OF DEFENDANTS' STOCK SALES

60. I reviewed the Form 4 Statements of Changes in Beneficial Ownership filed with the SEC by or on behalf of each of the following individuals: Dr. K. Peony Yu, Enrique Conterno, Pat Cotroneo, James Schoeneck, Thomas Neff, and Dr. Mark Eisner. I reviewed all Form 4s filed during the Class Period—defined in the CAC as December 20, 2018 through July 15, 2021, inclusive (CAC ¶ 2)—as well as those filed in the 31 months preceding the Class Period—from May 20, 2016 through, but not including, December 20, 2018 ("Pre-Class Period").

61. Based on my analysis, which is described in detail below, the following is a chart reflecting the sales of shares and resulting proceeds that each of these six individuals made during the Pre-Class Period and the Class Period:

	Pre-Class Period Sales (31 months)*		Class Period Sales (31 months)**		Difference	
Individual Shares		Proceeds	Shares	Proceeds	Shares	Proceeds
Neff	2,399,656	\$ 93,493,000	683,448	\$ 32,485,164	-1,716,208	-\$ 61,007,836
Yu	219,187	10,566,706	39,456	1,892,185	-179,731	-8,674,521
Cotroneo	335,434	15,806,720	149,226	6,916,508	-186,208	-8,890,212
Schoeneck	12,000	780,000	10,000	515,457	-2,000	-264,543
Conterno	N/A	N/A	N/A	N/A	N/A	N/A
Eisner	N/A	N/A	N/A	N/A	N/A	N/A
TOTAL	2,966,277	\$ 120,646,426	882,130	\$ 41,809,314	-2,084,147	-\$ 78,837,112
*(Shares Sold Betv	veen May 20, 201	6 - December 20, 2018)	**(Shares Sold I	Between December 20, 2	018 - July 15, 2021)	

- 62. I reviewed each Form 4, and I collected those Form 4s that reflected the sales of securities (not including stock withholding for tax liability, as explained further below). Conterno and Eisner did not have any such sales during either the Pre-Class Period or the Class Period.
- 63. I then created a worksheet to summarize the information for each sale by Yu, Cotroneo, Schoeneck, and Neff. Within the worksheet, I input the following information from each Form 4 (organized in chronological order) from both the Pre-Class and Class Period: Transaction Date, Filing Date, Shares Traded, Price of the Shares Traded, Proceeds, and whether it was pursuant

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to a 10b5-1 plan.

64. A sale of stock as reported to the SEC on Form 4 can include both a sale on the open market, or a withholding of securities for payment of a tax liability. I reviewed the CAC's allegations regarding the stock sales of each individual, and I determined that the CAC included information only for the sale of stock on the open market. I therefore did not include any stock sales that were coded on the Form 4 as an "F" transaction, which indicates stock sales in the form of tax withholding.

- 65. Next, to check my work, I reviewed the same information but provided through a vendor, Intelligize. Intelligize's "Insider Filings" module creates a similar set of worksheets as the ones I had produced through my own review. After downloading the worksheets through Intelligize, I then compared them against my own work to ensure the accuracy of each entry. The data from both sources were consistent.
- 66. The worksheets reflecting my work are reproduced as Appendices A-D to this Declaration. I have divided the sales into the Class Period and Pre-Class Period, using a gray-and-white color scheme to indicate Class Period sales and a blue-and-white color scheme to indicate Pre-Class Period Sales. Because Conterno and Eisner did not have any sales during either the Class Period or Pre-Class Period, I did not produce worksheets for them.
- 67. Moreover, the CAC alleges that Dr. Yu departed FibroGen on December 20, 2020. Accordingly, she was employed at FibroGen for only 24 of the 31 months of the Class Period (December 20, 2018 through December 20, 2020). I therefore did another set of calculations to analyze her stock sales during the 24 months prior to the beginning of the Class Period, and proceeds from shares sold during that 24 months period. Based on my analyses, during the 24 months preceding the Class Period, she sold 212,154 shares, for proceeds of \$10,432,445.
- 68. Likewise, the CAC alleges that Neff passed away in August 2019. Accordingly, he was only CEO during the first 8 months of the Class Period (from December 2018 through August 2019). I therefore did another set of calculations to analyze his stock sales during the 8 months prior to the Class Period, and proceeds from shares sold during that 8 months period. Based on my analysis, during the 8 months preceding the Class Period, he sold 584,904 shares for proceeds of

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\$32,256,719.76.

69. I also reviewed all the individuals' Form 4s to determine if each sale of stock on the open market or through private sale was made pursuant to a 10b5-1 trading plan. Based on my review, I determined that for Dr. K. Peony Yu, Pat Cotroneo, James Schoeneck, and Thomas Neff (the individuals who had sales during the Pre-Class Period or Class Period), each sale during the Class Period was executed pursuant to a 10b5-1 trading plan, as explicitly reflected in the

70. From my review as outlined above, Conterno's Form 4s indicated that he purchased shares on the open market on June 10 and June 11, 2020. The Form 4 reflecting this purchase is included in **Exhibit BBB**.

I declare under the penalty of perjury under the laws of the United States that the foregoing is true to the best of my knowledge.

Executed on this 14th day of January, 2022 in San Mateo, California.

explanatory footnotes in each Form 4 and highlighted for the Court's convenience.

/s/ Alexander J. Kasner
Alexander J. Kasner

Attorney for Defendants FibroGen, Inc., Enrique Conterno, James Schoeneck, Mark Eisner, and Pat Cotroneo

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Appendix A

Dr. K. Peony Yu Stock Sales Form 4 Sales (see Exhibit AAA)

Transaction Date	Filling Date	# Shares Sold	Price Per Share	Proceeds	10b5-1?
	5	CLASS PERIO			
12/16/2020	12/17/2020	3,350	\$41.61	\$139,394.00	✓
09/16/2020	09/18/2020	3,351	\$44.01	\$147,478.00	✓
09/03/2020	09/04/2020	10,000	\$50.89	\$508,900.00	✓
07/24/2020	07/28/2020	3,351	\$42.35	\$141,915.00	✓
12/16/2019	12/17/2019	3,420	\$46.68	\$159,646.00	✓
09/16/2019	09/18/2019	3,419	\$40.92	\$139,905.00	✓
06/14/2019	06/14/2019	3,420	\$40.96	\$140,083.00	✓
03/14/2019	03/15/2019	9,145	\$56.30	\$514,864.00	✓
Totals During	Class Period:	39,456		\$1,892,185.00	
		PRE-CLASS PER	OD SALES		
12/14/2018	12/18/2018	3,422	\$38.58	\$132,021.00	✓
07/03/2018	07/06/2018	15,645	\$65.00	\$1,016,920.00	✓
06/14/2018	06/15/2018	3,422	\$59.20	\$202,582.00	✓
04/16/2018	04/18/2018	4,100	\$47.39	\$194,299.00	✓
04/16/2018	04/18/2018	3,400	\$48.31	\$164,254.00	✓
03/14/2018	03/16/2018	9,891	\$53.20	\$526,201.00	✓
02/08/2018	02/09/2018	7,100	\$53.94	\$382,974.00	✓
02/08/2018	02/09/2018	400	\$54.51	\$21,804.00	✓
01/29/2018	01/31/2018	10,000	\$62.00	\$620,000.00	✓
12/14/2017	12/15/2017	2,851	\$43.70	\$124,589.00	✓
11/06/2017	11/08/2017	5,442	\$55.16	\$300,181.00	✓
11/06/2017	11/08/2017	2,058	\$55.91	\$115,063.00	✓
10/04/2017	10/06/2017	15,000	\$60.00	\$900,000.00	✓
10/02/2017	10/04/2017	11,000	\$53.90	\$592,900.00	✓
10/02/2017	10/04/2017	29,000	\$54.90	\$1,592,100.00	✓
09/14/2017	09/15/2017	2,851	\$51.00	\$145,401.00	✓
08/21/2017	08/23/2017	7,500	\$41.03	\$307,725.00	✓
08/08/2017	08/10/2017	32,400	\$50.50	\$1,636,200.00	✓
08/08/2017	08/10/2017	5,100	\$51.11	\$260,661.00	✓
08/01/2017	08/03/2017	10,000	\$33.48	\$334,800.00	✓
07/10/2017	07/11/2017	5,000	\$32.98	\$164,900.00	✓
06/14/2017	06/16/2017	3,721	\$28.95	\$107,723.00	✓
05/10/2017	05/12/2017	3,700	\$26.17	\$96,829.00	✓
05/10/2017	05/12/2017	1,300	\$26.97	\$35,061.00	✓
04/25/2017	04/27/2017	5,000	\$28.00	\$140,000.00	✓
03/14/2017	03/16/2017	4,651	\$25.13	\$116,898.00	✓
03/14/2017	03/16/2017	3,200	\$25.80	\$82,560.00	✓
01/10/2017	01/12/2017	5,000	\$23.56	\$117,800.00	✓
12/14/2016	12/16/2016	2,344	\$20.65	\$48,403.60	✓
09/14/2016	09/15/2016	2,345	\$18.66	\$43,757.70	✓
06/10/2016	06/14/2016	2,344	\$17.96	\$42,098.20	✓
Totals During Pr	e-Class Period:	219,187		\$10,566,705.50	

Appendix B

Pat Cotroneo Stock Sales

Form 4 Sales (see Exhibit CCC)

			Price Per					
Transaction Date	Filling Date	# Shares Sold	Share	Proceeds	10b5-1?			
CLASS PERIOD SALES								
06/15/2021	06/17/2021	4,053	\$25.62	\$103,838.00	✓			
12/15/2020	12/17/2020	3,068	\$43.60	\$133,765.00	✓			
09/15/2020	09/17/2020	3,070	\$43.63	\$133,944.00	✓			
09/03/2020	09/04/2020	15,004	\$50.91	\$763,854.00	✓			
08/07/2020	08/11/2020	22,554	\$48.00	\$1,082,590.00	✓			
06/16/2020	06/18/2020	3,928	\$39.68	\$155,863.00	✓			
03/16/2020	03/18/2020	9,239	\$26.36	\$243,540.00	✓			
12/20/2019	12/26/2019	46,727	\$45.51	\$2,126,550.00	✓			
12/20/2019	12/26/2019	12,729	\$46.27	\$588,971.00	✓			
09/17/2019	09/18/2019	3,201	\$41.38	\$132,457.00	✓			
06/18/2019	06/20/2019	3,201	\$43.12	\$138,027.00	✓			
03/19/2019	03/20/2019	7,665	\$55.41	\$424,718.00	✓			
02/28/2019	03/01/2019	14,787	\$60.08	\$888,391.00	✓			
Totals During		149,226	, , , , ,	6,916,508				
3 <u></u>		PRE-CLASS PERIO	OD SALES	.,,				
12/18/2018	12/20/2018	3,330	\$41.10	\$136,863.00	✓			
09/13/2018	09/14/2018	2,318	\$59.50	\$137,921.00	✓			
09/10/2018	09/12/2018	1,011	\$57.35	\$57,980.90	✓			
06/14/2018	06/15/2018	7,750	\$60.00	\$465,000.00	✓			
06/13/2018	06/15/2018	2,319	\$57.70	\$133,806.00	✓			
06/08/2018	06/08/2018	1,011	\$55.55	\$56,161.10	✓			
06/04/2018	06/05/2018	6,013	\$55.16	\$331,677.00	✓			
05/21/2018	05/23/2018	14,987	\$55.04	\$824,884.00	✓			
03/15/2018	03/15/2018	22,290	\$52.23	\$1,164,210.00	✓			
03/15/2018	03/15/2018	13,804	\$53.08	\$732,716.00	✓			
03/13/2018	03/15/2018	5,932	\$54.61	\$323,947.00	✓			
03/08/2018	03/08/2018	906	\$52.68	\$47,728.10	✓			
03/08/2018	03/08/2018	909	\$53.45	\$48,586.10	✓			
03/08/2018	03/08/2018	79	\$54.47	\$4,303.13	✓			
02/16/2018	02/16/2018	3,400	\$56.20	\$191,080.00	✓			
02/16/2018	02/16/2018	560	\$56.76	\$31,785.60	✓			
02/15/2018	02/16/2018	1,900	\$54.50	\$103,550.00	✓			
02/15/2018	02/16/2018	16,210	\$55.35	\$897,224.00	✓			
02/15/2018	02/16/2018	23,730	\$56.29	\$1,335,760.00	✓			
02/15/2018	02/16/2018	3,700	\$56.94	\$210,678.00	✓			
01/22/2018	01/24/2018	11,802	\$48.28	\$569,801.00	✓			
01/22/2018	01/24/2018	13,198	\$49.11	\$648,154.00	✓			
12/11/2017	12/13/2017	2,851	\$46.00	\$131,146.00	✓			
09/11/2017	09/13/2017	2,851	\$49.45	\$140,982.00	✓			
08/08/2017	08/10/2017	10,989	\$49.70	\$546,153.00	✓			
08/08/2017	08/10/2017	78,304	\$50.69	\$3,969,230.00	✓			
08/08/2017	08/10/2017	5,707	\$51.28	\$292,655.00	√			
08/02/2017	08/03/2017	20,746	\$34.13	\$708,061.00	✓			
08/01/2017	08/03/2017	7,600	\$33.54	\$254,904.00	✓			
07/06/2017	07/07/2017	4,000	\$34.00	\$136,000.00	✓			
06/22/2017	06/23/2017	3,000	\$32.00	\$96,000.00	✓			
06/19/2017	06/21/2017	5,500	\$30.00	\$165,000.00	✓			
06/12/2017	06/14/2017	2,891	\$28.75	\$83,116.20	✓			
04/25/2017	04/27/2017	6,500	\$28.00	\$182,000.00	✓			

			Price Per		
Transaction Date	Filling Date	# Shares Sold	Share	Proceeds	10b5-1?
03/10/2017	03/14/2017	7,851	\$25.30	\$198,630.00	✓
03/02/2017	03/06/2017	5,600	\$26.00	\$145,600.00	✓
03/01/2017	03/06/2017	900	\$26.00	\$23,400.00	✓
01/11/2017	01/13/2017	6,500	\$24.00	\$156,000.00	✓
12/12/2016	12/14/2016	2,344	\$22.05	\$51,685.20	✓
09/12/2016	09/14/2016	2,345	\$18.22	\$42,725.90	✓
06/15/2016	06/16/2016	1,796	\$16.49	\$29,616.00	✓
Totals During P	re-Class Period:	335,434		\$15,806,720.23	

Appendix C

James Schoeneck Stock Sales

Form 4 Sales (see Exhibit DDD)

			Price Per				
Transaction Date	Filling Date	# Shares Sold	Share	Proceeds	10b5-1?		
		CLASS PERIO	O SALES				
05/07/2019	05/09/2019	1,500	\$46.80	\$70,200.00	✓		
05/07/2019	05/09/2019	500	\$47.69	\$23,845.00	✓		
04/08/2019	04/10/2019	2,000	\$52.90	\$105,800.00	✓		
03/07/2019	03/08/2019	1,620	\$54.62	\$88,484.40	✓		
03/07/2019	03/08/2019	380	\$55.23	\$20,987.40	✓		
02/07/2019	02/08/2019	2,000	\$57.17	\$114,340.00	✓		
01/07/2019	01/09/2019	2,000	\$45.90	\$91,800.00	✓		
Totals During Class	Totals During Class Period:			\$515,456.80			
	PRE-CLASS PERIOD SALES						
07/03/2018	07/06/2018	7,639	\$65.00	\$496,535.00	✓		
06/22/2018	06/26/2018	4,361	\$65.00	\$283,465.00	✓		
Totals During Pre-0	Class Period:	12,000		\$780,000.00			

Appendix D

Thomas Neff Stock Sales

Form 4 Sales (see Exhibit EEE)

Troposition					
Transaction Date	Filling Date	# Shares Sold	Price Per Share	Proceeds	10b5-1?
Date	Filling Date	CLASS PERI		Proceeds	1005-17
08/22/2019	08/23/2019	17,100	\$43.80	\$748,980.00	√
08/22/2019	08/23/2019	1,300	\$44.73	\$58,149.00	<u> </u>
08/22/2019	08/23/2019	1,418	\$43.77	\$62.065.90	· ·
08/21/2019	08/23/2019	18,400	\$44.79	\$824,136.00	<u>·</u>
08/21/2019	08/23/2019	1,418	\$44.81	\$63,540.60	· ·
08/13/2019	08/14/2019	11,500	\$45.33	\$521,295.00	<u>·</u>
08/13/2019	08/14/2019	,	\$46.19	\$318,711.00	→
08/13/2019	08/14/2019	6,900	\$45.31	\$41,594.60	<u> </u>
08/13/2019	08/14/2019	918	\$46.17	\$23,085.00	▼
08/12/2019		500			<u> </u>
	08/14/2019	10,700	\$44.98	\$481,286.00	<u> </u>
08/12/2019	08/14/2019	7,700	\$45.59	\$351,043.00	<u> </u>
08/12/2019	08/14/2019	1,118	\$45.04	\$50,354.70	
08/12/2019	08/14/2019	300	\$45.67	\$13,701.00	√
07/25/2019	07/26/2019	16,500	\$46.86	\$773,190.00	√
07/25/2019	07/26/2019	1,900	\$47.72	\$90,668.00	√
07/25/2019	07/26/2019	1,318	\$46.80	\$61,682.40	√
07/25/2019	07/26/2019	100	\$47.90	\$4,790.00	√
07/24/2019	07/26/2019	18,400	\$46.54	\$856,336.00	√
07/24/2019	07/26/2019	1,418	\$46.57	\$66,036.30	√
07/11/2019	07/12/2019	17,900	\$45.14	\$808,006.00	✓
07/11/2019	07/12/2019	500	\$45.66	\$22,830.00	✓
07/11/2019	07/12/2019	1,418	\$45.09	\$63,937.60	✓
07/10/2019	07/12/2019	12,167	\$44.66	\$543,378.00	✓
07/10/2019	07/12/2019	6,233	\$45.07	\$280,921.00	✓
07/10/2019	07/12/2019	1,418	\$44.81	\$63,540.60	✓
06/20/2019	06/21/2019	16,200	\$44.28	\$717,336.00	✓
06/20/2019	06/21/2019	2,200	\$45.22	\$99,484.00	✓
06/20/2019	06/21/2019	1,318	\$44.23	\$58,295.10	✓
06/20/2019	06/21/2019	100	\$45.45	\$4,545.00	✓
06/19/2019	06/21/2019	18,400	\$44.02	\$809,968.00	✓
06/19/2019	06/21/2019	1,418	\$43.99	\$62,377.80	✓
06/06/2019	06/07/2019	6,900	\$37.57	\$259,233.00	✓
06/06/2019	06/07/2019	11,500	\$38.16	\$438,840.00	✓
06/06/2019	06/07/2019	800	\$37.77	\$30,216.00	✓
06/06/2019	06/07/2019	618	\$38.20	\$23,607.60	✓
06/05/2019	06/07/2019	16,878	\$38.43	\$648,622.00	✓
06/05/2019	06/07/2019	1,522	\$38.97	\$59,312.30	✓
06/05/2019	06/07/2019	1,418	\$38.52	\$54,621.40	✓
05/23/2019	05/24/2019	17,300	\$35.00	\$605,500.00	✓
05/23/2019	05/24/2019	1,100	\$35.25	\$38,775.00	✓
05/23/2019	05/24/2019	1,418	\$35.05	\$49,700.90	✓
05/22/2019	05/24/2019	18,400	\$35.73	\$657,432.00	✓
05/22/2019	05/24/2019	1,418	\$35.71	\$50,636.80	✓
05/14/2019	05/15/2019	6,350	\$36.40	\$231,140.00	✓
05/14/2019	05/15/2019	12,050	\$37.12	\$447,296.00	✓
05/14/2019	05/15/2019	1,100	\$36.77	\$40,447.00	✓
05/14/2019	05/15/2019	318	\$37.37	\$11,883.70	✓
05/13/2019	05/15/2019	6,200	\$35.23	\$218,426.00	✓
05/13/2019	05/15/2019	11,500	\$36.07	\$414,805.00	✓
05/13/2019	05/15/2019	700	\$36.92	\$25,844.00	✓

Transaction					
Date	Filling Date	# Shares Sold	Price Per Share	Proceeds	10b5-1?
05/13/2019	05/15/2019	918	\$35.52	\$32,607.40	✓
05/13/2019	05/15/2019	500	\$36.21	\$18,105.00	✓
04/18/2019	04/19/2019	3,217	\$45.69	\$146,985.00	√
04/18/2019	04/19/2019	8,625	\$46.82	\$403,822.00	✓
04/18/2019	04/19/2019	6,558	\$47.34	\$310,456.00	✓
04/18/2019	04/19/2019	200	\$45.33	\$9,066.00	✓
04/18/2019	04/19/2019	1,218	\$47.13	\$57,404.30	√
04/17/2019	04/19/2019	14,836	\$46.60	\$691,358.00	<u>√</u>
04/17/2019	04/19/2019	3,464	\$47.17	\$163,397.00	<u>√</u>
04/17/2019	04/19/2019	100	\$48.75	\$4,875.00	
04/17/2019	04/19/2019	1,318	\$46.60	\$61,418.80	<u>√</u>
04/17/2019	04/19/2019	100	\$47.09	\$4,709.00	<u>√</u>
04/04/2019	04/05/2019	13,900	\$53.17	\$739,063.00	<u>√</u>
04/04/2019	04/05/2019	2,700	\$54.24	\$146,448.00	<u> </u>
04/04/2019 04/04/2019	04/05/2019 04/05/2019	1,800	\$55.14 \$53.12	\$99,252.00	<u>√</u>
04/04/2019	04/05/2019	1,118 200	\$53.12	\$59,388.20 \$10,794.00	<u>√</u>
04/04/2019	04/05/2019	100	\$55.13	\$5,513.00	<u>√</u>
04/03/2019	04/05/2019	18,200	\$54.63	\$994,266.00	<u> </u>
04/03/2019	04/05/2019	200	\$55.24	\$11,048.00	<u> </u>
04/03/2019	04/05/2019	1,418	\$54.60	\$77,422.80	<u> </u>
03/21/2019	03/22/2019	9,642	\$55.37	\$533,878.00	<u>·</u> ✓
03/21/2019	03/22/2019	8,758	\$55.85	\$489,134.00	<u> </u>
03/21/2019	03/22/2019	1,418	\$55.83	\$79,166.90	<u>·</u>
03/20/2019	03/22/2019	11,134	\$55.14	\$613,929.00	· ·
03/20/2019	03/22/2019	7,266	\$55.83	\$405,661.00	√
03/20/2019	03/22/2019	428	\$55.09	\$23,578.50	✓
03/20/2019	03/22/2019	990	\$55.83	\$55,271.70	✓
03/07/2019	03/08/2019	17,200	\$54.90	\$944,280.00	✓
03/07/2019	03/08/2019	1,200	\$55.47	\$66,564.00	✓
03/07/2019	03/08/2019	1,318	\$54.89	\$72,345.00	✓
03/07/2019	03/08/2019	100	\$55.45	\$5,545.00	✓
03/06/2019	03/08/2019	9,464	\$55.84	\$528,470.00	✓
03/06/2019	03/08/2019	7,836	\$56.84	\$445,398.00	✓
03/06/2019	03/08/2019	1,100	\$57.68	\$63,448.00	✓
03/06/2019	03/08/2019	818	\$55.81	\$45,652.60	✓
03/06/2019	03/08/2019	600	\$56.86	\$34,116.00	✓
02/20/2019	02/21/2019	9,050	\$56.71	\$513,226.00	✓
02/20/2019	02/21/2019	9,850	\$57.47	\$566,080.00	✓
02/20/2019	02/21/2019	500	\$56.76	\$28,380.00	✓
02/20/2019	02/21/2019	418	\$57.41	\$23,997.40	✓
02/19/2019	02/21/2019	18,100	\$57.69	\$1,044,190.00	✓
02/19/2019	02/21/2019	800	\$58.26	\$46,608.00	✓
02/19/2019	02/21/2019	918	\$57.67	\$52,941.10	✓
02/08/2019	02/08/2019	5,257	\$56.54	\$297,231.00	√
02/08/2019	02/08/2019	13,593	\$57.05	\$775,481.00	√
02/08/2019	02/08/2019	50	\$57.68	\$2,884.00	√
02/08/2019	02/08/2019	818	\$56.79	\$46,454.20	<u>√</u>
02/08/2019	02/08/2019	100	\$57.68	\$5,768.00	√
02/07/2019	02/08/2019	19,015	\$55.94	\$1,063,700.00	<u>√</u>
02/07/2019	02/08/2019	5,013	\$57.06	\$286,042.00	<u>√</u>
02/07/2019	02/08/2019	3,847	\$55.98	\$215,355.00	<u>√</u>
02/07/2019	02/08/2019	487	\$57.01	\$27,763.90	<u> </u>
01/23/2019	01/24/2019	12,848	\$51.46	\$661,158.00	<u> </u>
01/23/2019	01/24/2019	12,975	\$52.37	\$679,501.00	<u> </u>
01/23/2019	01/24/2019	2,085	\$52.93	\$110,359.00	<u> </u>
01/23/2019	01/24/2019	702	\$51.83	\$36,384.70	· · · · · · · · · · · · · · · · · · ·

Transaction					
Date	Filling Date	# Shares Sold	Price Per Share	Proceeds	10b5-1?
01/23/2019	01/24/2019	1,390	\$52.59	\$73,100.10	✓
01/22/2019	01/24/2019	26,450	\$51.93	\$1,373,550.00	✓
01/22/2019	01/24/2019	3,550	\$52.42	\$186,091.00	✓
01/04/2019	01/07/2019	4,400	\$44.12	\$194,128.00	√
01/04/2019	01/07/2019	25,600	\$45.05	\$1,153,280.00	√
01/03/2019	01/07/2019	11,900	\$43.08	\$512,652.00	<u>√</u>
01/03/2019	01/07/2019	11,493	\$44.12	\$507,071.00	<u> </u>
01/03/2019 01/03/2019	01/07/2019	6,507 100	\$44.84 \$45.75	\$291,774.00 \$4,575.00	<u>√</u>
Total During Clas	* *	683,448	4 3.73	\$32,485,163.90	•
Total Baring Olas	ST CHOU.	PRE-CLASS PE	RIOD SALES	ψ02,400,100.00	
12/06/2018	12/06/2018	18,937	\$40.75	\$771,683.00	✓
12/06/2018	12/06/2018	9,227	\$41.29	\$380,983.00	✓
12/06/2018	12/06/2018	1,836	\$40.91	\$75,110.80	✓
11/21/2018	11/21/2018	18,900	\$39.47	\$745,983.00	✓
11/21/2018	11/21/2018	918	\$39.47	\$36,233.50	✓
11/20/2018	11/21/2018	2,700	\$38.29	\$103,383.00	✓
11/20/2018	11/21/2018	15,800	\$39.41	\$622,678.00	√
11/20/2018	11/21/2018	400	\$39.95	\$15,980.00	√
11/20/2018	11/21/2018	818	\$39.20	\$32,065.60	√
11/20/2018	11/21/2018	100	\$39.65	\$3,965.00	<u> </u>
11/02/2018 11/02/2018	11/02/2018	17,800 1,100	\$44.56 \$45.18	\$793,168.00 \$49,698.00	<u> </u>
11/02/2018	11/02/2018 11/02/2018	918	\$44.61	\$49,696.00	<u>√</u>
11/01/2018	11/02/2018	14,400	\$43.92	\$632,448.00	<u> </u>
11/01/2018	11/02/2018	4,500	\$44.42	\$199,890.00	<u>·</u>
11/01/2018	11/02/2018	918	\$44.08	\$40,465.40	✓
10/19/2018	10/19/2018	6,100	\$52.96	\$323,056.00	✓
10/19/2018	10/19/2018	6,300	\$53.74	\$338,562.00	✓
10/19/2018	10/19/2018	4,700	\$54.78	\$257,466.00	✓
10/19/2018	10/19/2018	1,800	\$55.57	\$100,026.00	✓
10/19/2018	10/19/2018	618	\$53.20	\$32,877.60	✓
10/19/2018	10/19/2018	300	\$54.69	\$16,407.00	✓
10/18/2018	10/19/2018	13,136	\$54.23	\$712,365.00	√
10/18/2018	10/19/2018	5,364	\$55.13	\$295,717.00	<u>√</u>
10/18/2018	10/19/2018	400	\$55.90	\$22,360.00	√
10/18/2018	10/19/2018	718	\$54.36	\$39,030.50	√
10/18/2018 10/03/2018	10/19/2018	200	\$55.29	\$11,058.00 \$481,912.00	<u>√</u>
10/03/2018	10/04/2018 10/04/2018	8,193 10,707	\$58.82 \$59.94	\$641,778.00	<u> </u>
10/03/2018	10/04/2018	307	\$58.68	\$18,014.80	<u> </u>
10/03/2018	10/04/2018	611	\$59.89	\$36,592.80	<u> </u>
10/02/2018	10/04/2018	8,998	\$58.47	\$526,113.00	✓
10/02/2018	10/04/2018	9,902	\$59.16	\$585,802.00	✓
10/02/2018	10/04/2018	718	\$58.79	\$42,211.20	✓
10/02/2018	10/04/2018	200	\$59.37	\$11,874.00	✓
09/20/2018	09/21/2018	1,291	\$57.36	\$74,051.80	✓
09/20/2018	09/21/2018	17,609	\$58.84	\$1,036,110.00	✓
09/20/2018	09/21/2018	9	\$57.64	\$518.76	✓
09/20/2018	09/21/2018	909	\$58.88	\$53,521.90	✓
09/19/2018	09/21/2018	11,408	\$56.45	\$643,982.00	√
09/19/2018	09/21/2018	7,492	\$57.50	\$430,790.00	√
09/19/2018	09/21/2018	710	\$56.71	\$40,264.10	√
09/19/2018	09/21/2018	208	\$57.48	\$11,955.80	<u>√</u>
09/07/2018	09/07/2018	15,495	\$56.60	\$877,017.00	<u>√</u>
09/07/2018 09/07/2018	09/07/2018 09/07/2018	3,405 718	\$57.44 \$56.58	\$195,583.00 \$40,624.40	<u>√</u>
09/01/2010	09/07/2018	/ 18	\$56.58	\$40,624.40	Y

Transaction					
Date	Filling Date	# Shares Sold	Price Per Share	Proceeds	10b5-1?
09/07/2018	09/07/2018	200	\$57.30	\$11,460.00	✓
09/06/2018	09/07/2018	12,480	\$57.73	\$720,470.00	✓
09/06/2018	09/07/2018	2,820	\$58.85	\$165,957.00	✓
09/06/2018	09/07/2018	3,600	\$59.77	\$215,172.00	✓
09/06/2018	09/07/2018	718	\$57.66	\$41,399.90	✓
09/06/2018	09/07/2018	200	\$59.08	\$11,816.00	✓
08/21/2018	08/22/2018	4,365	\$60.00	\$261,900.00	✓
08/21/2018	08/22/2018	14,535	\$60.71	\$882,420.00	✓
08/21/2018	08/22/2018	918	\$60.59	\$55,621.60	✓
08/20/2018	08/22/2018	14,897	\$59.83	\$891,288.00	✓
08/20/2018	08/22/2018	4,003	\$60.36	\$241,621.00	✓
08/20/2018	08/22/2018	918	\$59.82	\$54,914.80	✓
08/02/2018	08/03/2018	11,600	\$62.71	\$727,436.00	✓
08/02/2018	08/03/2018	7,300	\$63.19	\$461,287.00	✓
08/02/2018	08/03/2018	918	\$62.88	\$57,723.80	✓
08/01/2018	08/03/2018	13,660	\$62.95	\$859,897.00	✓
08/01/2018	08/03/2018	5,240	\$63.54	\$332,950.00	✓
08/01/2018	08/03/2018	918	\$63.08	\$57,907.40	✓
07/19/2018	07/20/2018	18,800	\$64.34	\$1,209,590.00	✓
07/19/2018	07/20/2018	100	\$64.80	\$6,480.00	✓
07/19/2018	07/20/2018	918	\$64.27	\$58,999.90	✓
07/18/2018	07/20/2018	8,100	\$65.19	\$528,039.00	✓
07/18/2018	07/20/2018	10,800	\$65.70	\$709,560.00	✓
07/18/2018	07/20/2018	918	\$65.48	\$60,110.60	✓
07/06/2018	07/06/2018	1,600	\$64.15	\$102,640.00	✓
07/06/2018	07/06/2018	5,940	\$65.24	\$387,526.00	✓
07/06/2018	07/06/2018	8,723	\$66.16	\$577,114.00	✓
07/06/2018	07/06/2018	2,637	\$66.96	\$176,574.00	✓
07/06/2018	07/06/2018	600	\$65.61	\$39,366.00	✓
07/06/2018	07/06/2018	318	\$66.80	\$21,242.40	✓
07/05/2018	07/06/2018	13,500	\$63.97	\$863,595.00	✓
07/05/2018	07/06/2018	5,400	\$64.62	\$348,948.00	✓
07/05/2018	07/06/2018	818	\$63.92	\$52,286.60	✓
07/05/2018	07/06/2018	100	\$64.75	\$6,475.00	✓
06/21/2018	06/22/2018	15,172	\$63.54	\$964,029.00	✓
06/21/2018	06/22/2018	3,728	\$64.08	\$238,890.00	✓
06/21/2018	06/22/2018	918	\$63.60	\$58,384.80	✓
06/20/2018	06/22/2018	7,701	\$63.31	\$487,550.00	✓
06/20/2018	06/22/2018	11,199	\$63.79	\$714,384.00	✓
06/20/2018	06/22/2018	798	\$63.55	\$50,712.90	✓
06/20/2018	06/22/2018	120	\$63.97	\$7,676.40	✓
06/05/2018	06/05/2018	16,200	\$54.93	\$889,866.00	✓
06/05/2018	06/05/2018	2,700	\$55.59	\$150,093.00	✓
06/05/2018	06/05/2018	918	\$54.94	\$50,434.90	✓
06/04/2018	06/05/2018	8,730	\$54.37	\$474,650.00	✓
06/04/2018	06/05/2018	10,170	\$54.99	\$559,248.00	✓
06/04/2018	06/05/2018	600	\$54.58	\$32,748.00	✓
06/04/2018	06/05/2018	318	\$55.21	\$17,556.80	✓
05/17/2018	05/18/2018	17,800	\$51.62	\$918,836.00	✓
05/17/2018	05/18/2018	1,100	\$52.26	\$57,486.00	✓
05/17/2018	05/18/2018	918	\$51.62	\$47,387.20	✓
05/16/2018	05/18/2018	9,890	\$51.71	\$511,412.00	✓
05/16/2018	05/18/2018	9,010	\$52.29	\$471,133.00	✓
05/16/2018	05/18/2018	918	\$52.04	\$47,772.70	✓
05/03/2018	05/04/2018	16,000	\$46.65	\$746,400.00	✓
05/03/2018	05/04/2018	2,900	\$47.30	\$137,170.00	✓
05/03/2018	05/04/2018	918	\$46.63	\$42,806.30	✓

Transaction					
Date	Filling Date	# Shares Sold	Price Per Share	Proceeds	10b5-1?
05/02/2018	05/04/2018	18,900	\$47.33	\$894,537.00	✓
05/02/2018	05/04/2018	918	\$47.32	\$43,439.80	✓
04/18/2018	04/18/2018	18,100	\$48.68	\$881,108.00	✓
04/18/2018	04/18/2018	800	\$49.22	\$39,376.00	✓
04/18/2018	04/18/2018	918	\$48.60	\$44,614.80	✓
04/17/2018	04/18/2018	5,200	\$47.94	\$249,288.00	✓
04/17/2018	04/18/2018	13,700	\$48.59	\$665,683.00	✓
04/17/2018	04/18/2018	918	\$48.54	\$44,559.70	√
04/05/2018	04/06/2018	10,500	\$45.13	\$473,865.00	√
04/05/2018	04/06/2018	8,400	\$46.20	\$388,080.00	√
04/05/2018	04/06/2018	618	\$45.06	\$27,847.10	√
04/05/2018	04/06/2018	300	\$46.10	\$13,830.00	<u>√</u>
04/04/2018	04/06/2018	10,100	\$45.16	\$456,116.00	<u>√</u>
04/04/2018	04/06/2018	7,800	\$45.97	\$358,566.00	<u>√</u>
04/04/2018	04/06/2018	1,000	\$46.68	\$46,680.00	<u> </u>
04/04/2018	04/06/2018	700 218	\$45.36	\$31,752.00	<u>√</u>
04/04/2018 03/21/2018	04/06/2018 03/22/2018	18,000	\$46.59 \$51.17	\$10,156.60 \$921,060.00	<u> </u>
		900	\$51.17 \$51.63		<u>√</u>
03/21/2018 03/21/2018	03/22/2018	918	\$51.03	\$46,467.00 \$46,937.30	<u> </u>
03/20/2018	03/22/2018	14,932	\$50.64	\$756,156.00	<u> </u>
03/20/2018	03/22/2018	3,968	\$50.04	\$202,447.00	<u> </u>
03/20/2018	03/22/2018	918	\$51.02	\$46,551.80	<u> </u>
03/08/2018	03/08/2018	6,400	\$50.71	\$337,536.00	<u> </u>
03/08/2018	03/08/2018	11,800	\$53.44	\$630,592.00	<u> </u>
03/08/2018	03/08/2018	700	\$54.09	\$37,863.00	<u> </u>
03/08/2018	03/08/2018	300	\$52.55	\$15,765.00	<u> </u>
03/08/2018	03/08/2018	618	\$53.59	\$33,118.60	<u>·</u>
03/07/2018	03/08/2018	8,802	\$52.58	\$462,809.00	· ✓
03/07/2018	03/08/2018	7,800	\$53.26	\$415,428.00	√
03/07/2018	03/08/2018	2,298	\$54.14	\$124,414.00	✓
03/07/2018	03/08/2018	700	\$52.82	\$36,974.00	✓
03/07/2018	03/08/2018	218	\$53.91	\$11,752.40	✓
02/23/2018	02/23/2018	11,400	\$55.90	\$637,260.00	✓
02/23/2018	02/23/2018	6,500	\$56.89	\$369,785.00	✓
02/23/2018	02/23/2018	1,000	\$57.40	\$57,400.00	✓
02/23/2018	02/23/2018	500	\$55.79	\$27,895.00	✓
02/23/2018	02/23/2018	418	\$57.11	\$23,872.00	✓
02/22/2018	02/23/2018	8,749	\$56.50	\$494,318.00	✓
02/22/2018	02/23/2018	10,051	\$57.43	\$577,229.00	✓
02/22/2018	02/23/2018	100	\$58.03	\$5,802.50	✓
02/22/2018	02/23/2018	618	\$56.50	\$34,917.00	✓
02/22/2018	02/23/2018	300	\$57.72	\$17,316.00	✓
01/30/2018	01/31/2018	10,000	\$60.81	\$608,100.00	✓
01/30/2018	01/31/2018	8,700	\$61.54	\$535,398.00	✓
01/30/2018	01/31/2018	200	\$62.49	\$12,498.00	✓
01/30/2018	01/31/2018	418	\$61.28	\$25,615.00	✓
01/29/2018	01/31/2018	200	\$59.30	\$11,860.00	√
01/29/2018	01/31/2018	4,500	\$61.06	\$274,770.00	√
01/29/2018	01/31/2018	13,800	\$61.82	\$853,116.00	<u>√</u>
01/29/2018	01/31/2018	400	\$62.43	\$24,972.00	<u>√</u>
01/29/2018	01/31/2018	418	\$61.64	\$25,765.50	√
01/19/2018	01/19/2018	15,200	\$47.18	\$717,136.00	√
01/19/2018	01/19/2018	3,700	\$47.68	\$176,416.00	<u>√</u>
01/19/2018	01/19/2018	418	\$47.11	\$19,692.00	<u>√</u>
01/18/2018	01/19/2018	14,658	\$47.56	\$697,134.00	√
01/18/2018	01/19/2018	4,242	\$47.92	\$203,277.00	✓

Transaction					
Date	Filling Date	# Shares Sold	Price Per Share	Proceeds	10b5-1?
01/18/2018	01/19/2018	418	\$47.51	\$19,859.20	✓
01/05/2018	01/08/2018	10,800	\$45.84	\$495,072.00	✓
01/05/2018	01/08/2018	6,698	\$46.97	\$314,605.00	✓
01/05/2018	01/08/2018	1,402	\$47.60	\$66,735.20	✓
01/05/2018	01/08/2018	418	\$45.84	\$19,161.10	✓
01/04/2018	01/08/2018	4,018	\$47.92	\$192,543.00	✓
01/04/2018	01/08/2018	13,082	\$49.04	\$641,541.00	✓
01/04/2018	01/08/2018	1,800	\$49.70	\$89,460.00	√
01/04/2018	01/08/2018	418	\$48.89	\$20,436.00	√
12/29/2017	01/02/2018	9,087	\$48.06	\$436,721.00	√
12/29/2017	01/02/2018	9,813	\$48.88	\$479,659.00	√
12/29/2017	01/02/2018	418	\$48.36	\$20,214.50	√
12/28/2017	01/02/2018	18,550	\$48.28	\$895,594.00	<u>√</u>
12/28/2017	01/02/2018	350	\$48.72	\$17,052.00	<u>√</u>
12/28/2017	01/02/2018	418	\$48.30	\$20,189.40	<u> </u>
12/21/2017	12/22/2017	9,377	\$44.92	\$421,215.00	<u> </u>
12/21/2017	12/22/2017	9,523	\$45.52	\$433,487.00	<u> </u>
12/21/2017 12/20/2017	12/22/2017	418 7,071	\$45.22 \$43.66	\$18,902.00 \$308,720.00	<u> </u>
12/20/2017	12/22/2017 12/22/2017	11,829	\$44.39		<u> </u>
12/20/2017	12/22/2017	418	\$43.64	\$525,089.00 \$18,241.50	<u> </u>
12/15/2017	12/15/2017	10,552	\$41.37	\$436,536.00	<u> </u>
12/15/2017	12/15/2017	8,048	\$42.07	\$338,579.00	<u> </u>
12/15/2017	12/15/2017	300	\$42.78	\$12,834.00	<u>√</u>
12/15/2017	12/15/2017	418	\$41.49	\$17,342.80	<u> </u>
12/14/2017	12/15/2017	6,918	\$42.18	\$291,801.00	<u> </u>
12/14/2017	12/15/2017	11,782	\$43.01	\$506,744.00	<u>·</u>
12/14/2017	12/15/2017	200	\$43.60	\$8,720.00	· ✓
12/14/2017	12/15/2017	360	\$42.09	\$15,152.40	✓
12/14/2017	12/15/2017	58	\$43.08	\$2,498.64	√
11/17/2017	11/17/2017	16,000	\$46.60	\$745,600.00	✓
11/17/2017	11/17/2017	2,900	\$46.98	\$136,242.00	✓
11/17/2017	11/17/2017	418	\$46.75	\$19,541.50	✓
11/16/2017	11/17/2017	4,000	\$45.62	\$182,480.00	✓
11/16/2017	11/17/2017	11,900	\$46.67	\$555,373.00	✓
11/16/2017	11/17/2017	3,000	\$47.62	\$142,860.00	✓
11/16/2017	11/17/2017	418	\$46.75	\$19,541.50	✓
10/31/2017	11/01/2017	12,200	\$55.62	\$678,564.00	✓
10/31/2017	11/01/2017	6,700	\$56.23	\$376,741.00	✓
10/31/2017	11/01/2017	418	\$55.95	\$23,387.10	✓
10/30/2017	11/01/2017	6,782	\$55.79	\$378,368.00	✓
10/30/2017	11/01/2017	9,918	\$56.65	\$561,855.00	✓
10/30/2017	11/01/2017	2,200	\$57.36	\$126,192.00	✓
10/30/2017	11/01/2017	408	\$55.82	\$22,774.60	✓
10/30/2017	11/01/2017	10	\$56.75	\$567.50	√
10/17/2017	10/18/2017	4,200	\$54.69	\$229,698.00	✓
10/17/2017	10/18/2017	14,700	\$55.38	\$814,086.00	√
10/17/2017	10/18/2017	100	\$55.10	\$5,510.00	<u>√</u>
10/17/2017	10/18/2017	318	\$55.25	\$17,569.50	√
10/16/2017	10/18/2017	12,294	\$54.54	\$670,515.00	<u>√</u>
10/16/2017	10/18/2017	6,606	\$55.37	\$365,774.00	√
10/16/2017	10/18/2017	417	\$54.35	\$22,663.90	√
10/16/2017	10/18/2017	1 10 000	\$55.45	\$55.45	√
10/03/2017	10/04/2017	18,900	\$55.71	\$1,052,920.00	<u>√</u>
10/03/2017	10/04/2017	318	\$55.95	\$17,792.10	<u>√</u>
10/03/2017	10/04/2017	100	\$55.65 \$54.42	\$5,565.00 \$514.140.00	
10/02/2017	10/04/2017	9,500	\$54.12	\$514,140.00	✓

Transaction					
Date	Filling Date	# Shares Sold	Price Per Share	Proceeds	10b5-1?
10/02/2017	10/04/2017	9,400	\$54.78	\$514,932.00	✓
10/02/2017	10/04/2017	318	\$55.30	\$17,585.40	✓
10/02/2017	10/04/2017	100	\$53.80	\$5,380.00	✓
09/20/2017	09/21/2017	18,900	\$53.69	\$1,014,740.00	✓
09/20/2017	09/21/2017	418	\$53.48	\$22,354.60	√
09/19/2017	09/21/2017	18,001	\$53.22	\$958,013.00	√
09/19/2017	09/21/2017	899	\$53.71	\$48,285.30	√
09/19/2017	09/21/2017	418	\$52.85	\$22,091.30	<u>√</u>
09/14/2017	09/15/2017	1,500	\$50.89	\$76,335.00	<u>√</u>
09/14/2017	09/15/2017	12,000	\$51.99	\$623,880.00	<u>√</u>
09/14/2017	09/15/2017	5,400	\$52.47	\$283,338.00	<u> </u>
09/14/2017 09/14/2017	09/15/2017 09/15/2017	318 100	\$52.08 \$51.55	\$16,559.80 \$5,155.00	<u>√</u>
09/13/2017	09/15/2017	4,900	\$50.33	\$246,617.00	<u>√</u>
09/13/2017	09/15/2017	11,500	\$51.52	\$592,480.00	<u> </u>
09/13/2017	09/15/2017	2,500	\$51.32	\$130,325.00	<u> </u>
09/13/2017	09/15/2017	318	\$51.75	\$16,456.50	<u>·</u> ✓
09/13/2017	09/15/2017	100	\$51.73	\$5,127.50	<u> </u>
08/29/2017	08/30/2017	3,100	\$43.43	\$134,633.00	<u> </u>
08/29/2017	08/30/2017	15,800	\$44.60	\$704,680.00	<u>·</u>
08/29/2017	08/30/2017	418	\$44.64	\$18,659.50	√
08/28/2017	08/30/2017	18,900	\$43.04	\$813,456.00	√
08/28/2017	08/30/2017	418	\$43.10	\$18,015.80	✓
07/25/2017	07/26/2017	18,900	\$35.12	\$663,768.00	✓
07/25/2017	07/26/2017	418	\$35.11	\$14,676.00	✓
07/24/2017	07/26/2017	18,900	\$35.06	\$662,634.00	✓
07/24/2017	07/26/2017	418	\$35.09	\$14,667.60	✓
07/07/2017	07/07/2017	18,900	\$33.22	\$627,858.00	✓
07/07/2017	07/07/2017	418	\$33.24	\$13,894.30	✓
07/06/2017	07/07/2017	9,300	\$33.27	\$309,411.00	✓
07/06/2017	07/07/2017	9,600	\$33.79	\$324,384.00	✓
07/06/2017	07/07/2017	218	\$33.23	\$7,244.14	✓
07/06/2017	07/07/2017	200	\$33.78	\$6,756.00	✓
06/22/2017	06/23/2017	16,700	\$31.82	\$531,394.00	✓
06/22/2017	06/23/2017	2,200	\$32.31	\$71,082.00	✓
06/22/2017	06/23/2017	418	\$32.02	\$13,384.40	✓
06/21/2017	06/23/2017	18,900	\$31.15	\$588,735.00	✓
06/21/2017	06/23/2017	418	\$31.22	\$13,050.00	√
06/16/2017	06/19/2017	18,900	\$29.54	\$558,306.00	✓
06/16/2017	06/19/2017	418	\$29.58	\$12,364.40	√
06/15/2017	06/19/2017	18,900	\$29.25	\$552,825.00	√
06/15/2017	06/19/2017	418	\$29.28	\$12,239.00	√
05/31/2017	06/01/2017	18,900	\$25.97	\$490,833.00	√
05/31/2017	06/01/2017	418	\$26.03	\$10,880.50	<u>√</u>
05/30/2017	06/01/2017	11,400	\$26.16	\$298,224.00	<u> </u>
05/30/2017	06/01/2017	7,500	\$26.88	\$201,600.00	<u>√</u>
05/30/2017	06/01/2017	418	\$26.30 \$27.64	\$10,993.40	<u> </u>
05/16/2017 05/16/2017	05/17/2017 05/17/2017	18,900 418	\$27.64 \$27.67	\$522,396.00 \$11,566.10	<u> </u>
05/15/2017	05/17/2017	18,900	\$27.07	\$524,475.00	<u>√</u>
05/15/2017	05/17/2017	418	\$27.73	\$11,624.60	<u> </u>
04/25/2017	04/26/2017	18,900	\$27.49	\$519,561.00	<u>√</u>
04/25/2017	04/26/2017	418	\$27.67	\$11,566.10	<u> </u>
04/24/2017	04/26/2017	18,900	\$26.35	\$498,015.00	<u>·</u>
04/24/2017	04/26/2017	418	\$26.45	\$11,056.10	<u>·</u> ✓
04/13/2017	04/14/2017	18,900	\$24.91	\$470,799.00	<u>·</u>
04/13/2017	04/14/2017	418	\$24.95	\$10,429.10	✓
07/10/2017	07/17/2017	410	φ <u>ζ</u> 4.30	ψ10, 4 23.10	•

Transaction					
Date	Filling Date	# Shares Sold	Price Per Share	Proceeds	10b5-1?
04/12/2017	04/14/2017	16,600	\$24.58	\$408,028.00	✓
04/12/2017	04/14/2017	2,300	\$25.28	\$58,144.00	✓
04/12/2017	04/14/2017	418	\$24.57	\$10,270.30	✓
04/04/2017	04/04/2017	18,900	\$23.85	\$450,765.00	✓
04/04/2017	04/04/2017	418	\$23.80	\$9,948.40	✓
04/03/2017	04/04/2017	18,900	\$23.99	\$453,411.00	✓
04/03/2017	04/04/2017	418	\$23.92	\$9,998.56	✓
03/21/2017	03/22/2017	13,800	\$23.51	\$324,438.00	✓
03/21/2017	03/22/2017	4,700	\$24.54	\$115,338.00	✓
03/21/2017	03/22/2017	400	\$25.06	\$10,024.00	✓
03/21/2017	03/22/2017	418	\$23.58	\$9,856.44	✓
03/20/2017	03/22/2017	18,900	\$24.88	\$470,232.00	✓
03/20/2017	03/22/2017	418	\$24.92	\$10,416.60	✓
03/15/2017	03/16/2017	18,900	\$25.07	\$473,823.00	✓
03/15/2017	03/16/2017	418	\$25.26	\$10,558.70	✓
03/14/2017	03/16/2017	18,400	\$25.04	\$460,736.00	✓
03/14/2017	03/16/2017	500	\$25.79	\$12,895.00	✓
03/14/2017	03/16/2017	418	\$25.02	\$10,458.40	✓
02/14/2017	02/15/2017	18,900	\$23.90	\$451,710.00	✓
02/14/2017	02/15/2017	418	\$23.89	\$9,986.02	✓
02/13/2017	02/15/2017	18,900	\$23.97	\$453,033.00	✓
02/13/2017	02/15/2017	418	\$24.01	\$10,036.20	✓
02/09/2017	02/10/2017	18,899	\$23.89	\$451,497.00	✓
02/08/2017	02/10/2017	18,899	\$23.03	\$435,244.00	✓
01/27/2017	01/27/2017	18,899	\$23.16	\$437,701.00	✓
01/26/2017	01/27/2017	18,899	\$23.42	\$442,615.00	✓
01/12/2017	01/13/2017	9,700	\$23.77	\$230,569.00	✓
01/12/2017	01/13/2017	9,199	\$24.65	\$226,755.00	✓
01/11/2017	01/13/2017	10,400	\$23.18	\$241,072.00	✓
01/11/2017	01/13/2017	8,499	\$23.90	\$203,126.00	✓
12/28/2016	12/29/2016	18,899	\$20.69	\$391,020.00	✓
12/27/2016	12/29/2016	18,899	\$20.79	\$392,910.00	✓
12/13/2016	12/14/2016	16,774	\$20.94	\$351,248.00	✓
12/13/2016	12/14/2016	2,125	\$21.46	\$45,602.50	✓
12/12/2016	12/14/2016	17,999	\$21.45	\$386,079.00	✓
12/12/2016	12/14/2016	900	\$22.11	\$19,899.00	✓
11/29/2016	11/30/2016	18,899	\$22.86	\$432,031.00	✓
11/28/2016	11/30/2016	18,899	\$22.74	\$429,763.00	✓
11/17/2016	11/18/2016	18,899	\$22.22	\$419,936.00	✓
11/16/2016	11/18/2016	18,899	\$22.36	\$422,582.00	✓
11/01/2016	11/01/2016	18,899	\$16.84	\$318,259.00	✓
10/31/2016	11/01/2016	18,899	\$16.67	\$315,046.00	✓
10/19/2016	10/19/2016	18,899	\$17.56	\$331,866.00	✓
10/18/2016	10/19/2016	18,899	\$17.94	\$339,048.00	✓
10/04/2016	10/05/2016	18,899	\$20.67	\$390,642.00	✓
10/03/2016	10/05/2016	18,899	\$20.55	\$388,374.00	✓
09/21/2016	09/22/2016	18,899	\$21.52	\$406,706.00	✓
09/20/2016	09/22/2016	18,899	\$21.80	\$411,998.00	✓
09/09/2016	09/09/2016	18,899	\$18.83	\$355,868.00	✓
09/08/2016	09/09/2016	18,899	\$19.14	\$361,727.00	✓
08/26/2016	08/29/2016	18,899	\$17.81	\$336,591.00	✓
08/25/2016	08/29/2016	17,699	\$17.76	\$314,334.00	✓
08/25/2016	08/29/2016	1,200	\$18.15	\$21,780.00	✓
07/27/2016	07/28/2016	18,899	\$18.41	\$347,885.00	✓
07/26/2016	07/28/2016	14,799	\$18.28	\$270,526.00	√
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07/26/2016	07/28/2016	4,100	\$18.57	\$76,137.00	✓

Transaction					
Date	Filling Date	# Shares Sold	Price Per Share	Proceeds	10b5-1?
07/13/2016	07/14/2016	10,800	\$17.24	\$186,192.00	✓
07/12/2016	07/14/2016	13,500	\$17.81	\$240,435.00	✓
06/29/2016	06/30/2016	13,500	\$16.17	\$218,295.00	✓
06/28/2016	06/30/2016	13,400	\$15.87	\$212,658.00	✓
06/28/2016	06/30/2016	100	\$16.21	\$1,621.00	✓
06/15/2016	06/16/2016	13,500	\$16.49	\$222,615.00	✓
06/14/2016	06/16/2016	13,500	\$16.47	\$222,345.00	✓
06/03/2016	06/03/2016	13,500	\$18.81	\$253,935.00	✓
06/02/2016	06/03/2016	13,500	\$19.16	\$258,660.00	✓
05/20/2016	05/20/2016	13,500	\$17.88	\$241,380.00	✓
Total During Pre-	Class Period:	2,399,656		\$93,493,000.51	•

EXHIBIT A

UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

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 ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2017

OR

☐ TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from to. Commission file number: 001-36740

FIBROGEN, INC.

(Exact name of registrant as specified in its charter)

Delaware 77-0357827

(State or other jurisdiction of incorporation or organization)

(I.R.S. Employer Identification No.)

409 Illinois Street

San Francisco, CA

94158

(Address of principal executive offices)

(zip code)

Registrant's telephone number, including area code: (415) 978-1200

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class
Common Stock, \$0.01 par value

Name of Exchange on Which Registered
The NASDAQ Global Select Market

Securities registered pursuant to Section 12(g) of the Act:

None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes \boxtimes No \square

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes \square No \boxtimes

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes \boxtimes No \square

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes \boxtimes No \square

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act:

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

Indicate by check mark whether the registrant is a shell company (as defined in Exchange Act Rule 12b-2). Yes \square No \boxtimes

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant, computed by reference to the closing price as of the last business day of the registrant's most recently completed second fiscal quarter, June 30, 2017, was approximately \$1,674.4 million. Shares of Common Stock held by each executive officer and director and stockholders known by the registrant to own 10% or more of the outstanding stock based on public filings and other information known to the registrant have been excluded since such persons may be deemed affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

The number of shares of common stock outstanding as of January 31, 2018 was 82,666,979.

DOCUMENTS INCORPORATED BY REFERENCE

Items 10, 11, 12, 13 and 14 of Part III of this Annual Report on Form 10-K incorporate information by reference from the definitive proxy statement for the registrant's 2018 Annual Meeting of Stockholders to be filed with the Securities and Exchange Commission pursuant to Regulation 14A not later than after 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K.

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FORWARD-LOOKING STATEMENTS

This Annual Report filed on Form 10-K and the information incorporated herein by reference, particularly in the sections captioned "Risk Factors," "Management's Discussion and Analysis of Financial Condition and Results of Operations" and "Business," contains forwardlooking statements, which involve substantial risks and uncertainties. In this Annual Report, all statements other than statements of historical or present facts contained in this Annual Report, including statements regarding our future financial condition, business strategy and plans and objectives of management for future operations, are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "believe," "will," "may," "estimate," "continue," "anticipate," "contemplate," "intend," "target," "project," "should," "plan," "expect," "predict," "could," "potentially" or the negative of these terms or other similar terms or expressions that concern our expectations, strategy, plans or intentions. Forward-looking statements appear in a number of places throughout this Annual Report and include statements regarding our intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things, our ongoing and planned preclinical development and clinical trials, the timing of and our ability to make regulatory filings and obtain and maintain regulatory approvals for roxadustat, pamrevlumab and our other product candidates, our intellectual property position, the potential safety, efficacy, reimbursement, convenience clinical and pharmaco-economic benefits of our product candidates, the potential markets for any of our product candidates, our ability to develop commercial functions, our ability to operate in China, expectations regarding clinical trial data, our results of operations, cash needs, spending of the proceeds from our initial public offering and the concurrent private placement, financial condition, liquidity, prospects, growth and strategies, the industry in which we operate and the trends that may affect the industry or us. We have based these forward-looking statements largely on our current expectations and projections about future events and financial trends that we believe may affect our financial condition, results of operations, business strategy and financial needs. These forward-looking statements are subject to a number of risks, uncertainties and assumptions described in the section of this Annual Report captioned "Risk Factors" and elsewhere in this Annual Report.

These risks are not exhaustive. Other sections of this Annual Report may include additional factors that could adversely impact our business and financial performance. Moreover, we operate in a very competitive and rapidly changing environment. New risk factors emerge from time to time, and it is not possible for our management to predict all risk factors nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements.

You should not rely upon forward-looking statements as predictions of future events. We cannot assure you that the events and circumstances reflected in the forward-looking statements will be achieved or occur. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements. The forward-looking statements made in this Annual Report are based on circumstances as of the date on which the statements are made. Except as required by law, we undertake no obligation to update publicly any forward-looking statements for any reason after the date of this Annual Report or to conform these statements to actual results or to changes in our expectations.

This Annual Report also contains market data, research, industry forecasts and other similar information obtained from or based on industry reports and publications, including information concerning our industry, our business, and the potential markets for our product candidates, including data regarding the estimated size and patient populations of those and related markets, their projected growth rates and the incidence of certain medical conditions, as well as physician and patient practices within the related markets. Such data and information involve a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates.

You should read this Annual Report with the understanding that our actual future results, levels of activity, performance and achievements may be materially different from what we expect. We qualify all of our forward-looking statements by these cautionary statements.

ITEM 1A. RISK FACTORS

Investing in our common stock involves a high degree of risk. You should carefully consider the risks described below in addition to the other information included or incorporated by reference in this Annual Report on Form 10-K, including our consolidated financial statements and the related notes and "Management's Discussion and Analysis of Financial Condition and Results of Operations," before deciding whether to invest in our common stock. The occurrence of any of the events or developments described below could harm our business, financial condition, results of operations and growth prospects. In such an event, the market price of our common stock could decline, and you may lose all or part of your investment. Although we have discussed all known material risks, the risks described below are not the only ones that we may face. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also impair our business operations.

Risks Related to Our Financial Condition and History of Operating Losses

We have incurred significant losses since our inception and anticipate that we will continue to incur losses for the foreseeable future and may never achieve or sustain profitability. We may require additional financings in order to fund our operations.

We are a clinical-stage biopharmaceutical company with two lead product candidates in clinical development, roxadustat in anemia in chronic kidney disease ("CKD") and pamrevlumab (FG-3019), in idiopathic pulmonary fibrosis ("IPF"), pancreatic cancer, and Duchenne muscular dystrophy ("DMD"). Pharmaceutical product development is a highly risky undertaking. To date, we have focused our efforts and most of our resources on hypoxia-inducible factor ("HIF"), and fibrosis biology research, as well as developing our lead product candidates. We are not profitable and, other than in 2006 and 2007 due to income received from our Astellas Pharma Inc. ("Astellas") collaboration, have incurred losses in each year since our inception. We have not generated any significant revenue based on product sales to date. We continue to incur significant research and development and other expenses related to our ongoing operations. Our net loss for the years ended December 31, 2017, 2016 and 2015 was approximately \$126.2 million, \$61.7 million and \$85.8 million, respectively. As of December 31, 2017, we had an accumulated deficit of \$595.9 million. As of December 31, 2017, we had capital resources consisting of cash, cash equivalents and short-term investments of \$735.7 million plus \$10.5 million of long-term investments classified as available for sale securities. Despite contractual development and cost coverage commitments from our collaboration partners, AstraZeneca AB ("AstraZeneca") and Astellas, and the potential to receive milestone and other payments from these partners, we anticipate we will continue to incur losses for the foreseeable future, and we anticipate these losses will increase as we continue our development of, and seek regulatory approval for our product candidates. If we do not successfully develop and obtain regulatory approval for our existing or any future product candidates and effectively manufacture, market and sell any product candidates that are approved, we may never generate product sales, and even if we do generate product sales, we may never achieve or sustain profitability on a quarterly or annual basis. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our stockholders' equity and working capital. Our failure to become and remain profitable would depress the market price of our common stock and could impair our ability to raise capital, expand our business, diversify our product offerings or continue our operations.

We believe that we will continue to expend substantial resources for the foreseeable future as we continue late-stage clinical development of roxadustat, grow our operations in the People's Republic of China ("China"), expand our clinical development efforts on pamrevlumab, seek regulatory approval, prepare for the commercialization of our product candidates, and pursue additional indications. These expenditures will include costs associated with research and development, conducting preclinical trials and clinical trials, obtaining regulatory approvals in various jurisdictions, and manufacturing and supplying products and product candidates for ourselves and our partners. In particular, in our planned Phase 3 clinical trial program for roxadustat, which we believe will be the largest Phase 3 program ever conducted for an anemia product candidate, we are expecting to enroll more than 8,000 patients for our U.S. and European programs alone. We are conducting this Phase 3 program in conjunction with Astellas and AstraZeneca, and we are substantially dependent on Astellas and AstraZeneca for the funding of this large program. The outcome of any clinical trial and/or regulatory approval process is highly uncertain and we are unable to fully estimate the actual costs necessary to successfully complete the development and regulatory approval process for our compounds in development and any future product candidates. We believe that the net proceeds from our 2017 public offerings, our existing cash and cash equivalents, short-term and long-term investments and accounts receivable, and expected third party collaboration revenues will allow us to fund our operating plans through at least the next 12 months. Our operating plans or third party collaborations may change as a result of many factors, which are discussed in more detail below, and other factors that may not currently be known to us, and we therefore may need to seek additional funds sooner than planned, through offerings of public or private securities, debt financings or other sources, such as royalty monetization or other structured financings. Such financings may result in dilution to stockholders, imposition of debt covenants and repayment obligations, or other restrictions that may adversely affect our business. We may also seek additional capital due to favorable market conditions or strategic considerations even if we currently believe that we have sufficient funds for our current or future operating plans.

Our future funding requirements will depend on many factors, including, but not limited to:

- the rate of progress in the development of our product candidates;
- the costs of development efforts for our product candidates, such as pamrevlumab, that are not subject to reimbursement from our collaboration partners;
- the costs necessary to obtain regulatory approvals, if any, for our product candidates in the United States ("U.S."), China and other jurisdictions, and the costs of post-marketing studies that could be required by regulatory authorities in jurisdictions where approval is obtained;
- the continuation of our existing collaborations and entry into new collaborations;
- the time and unreimbursed costs necessary to commercialize products in territories in which our product candidates are approved for sale;
- the revenues from any future sales of our products as well as revenue earned from profit share, royalties and milestones;
- the level of reimbursement or third party payor pricing available to our products;
- the costs of establishing and maintaining manufacturing operations and obtaining third party commercial supplies of our products, if any, manufactured in accordance with regulatory requirements;
- the costs we incur in maintaining domestic and foreign operations, including operations in China;
- regulatory compliance costs; and
- the costs we incur in the filing, prosecution, maintenance and defense of our extensive patent portfolio and other intellectual property rights.

Additional funds may not be available when we require them, or on terms that are acceptable to us. If adequate funds are not available to us on a timely basis, we may be required to delay, limit, reduce or terminate our research and development efforts or other operations or activities that may be necessary to commercialize our product candidates.

All of our recent revenue has been earned from collaboration partners for our product candidates under development.

During the years ended December 2017, 2016 and 2015, substantially all of our revenues recognized were from our collaboration partners.

We will require substantial additional capital to achieve our development and commercialization goals, which for our lead product candidate, roxadustat, is currently contemplated to be provided under our existing third party collaborations with Astellas and AstraZeneca.

If either or both of these collaborations were to be terminated, we could require significant additional capital in order to proceed with development and commercialization of our product candidates, or we may require additional partnering in order to help fund such development and commercialization. If adequate funds or partners are not available to us on a timely basis or on favorable terms, we may be required to delay, limit, reduce or terminate our research and development efforts or other operations.

If we are unable to continue to progress our development efforts and achieve milestones under our collaboration agreements, our revenues may decrease and our activities may fail to lead to commercial products.

Substantially all of our revenues to date have been, and a significant portion of our future revenues are expected to be, derived from our existing collaboration agreements. Revenues from research and development collaborations depend upon continuation of the collaborations, reimbursement of development costs, the achievement of milestones and royalties and profits from our product sales, if any, derived from future products developed from our research. If we are unable to successfully advance the development of our product candidates or achieve milestones, revenues under our collaboration agreements will be substantially less than expected.

Risks Related to the Development and Commercialization of Our Product Candidates

We are substantially dependent on the success of our lead product candidate, roxadustat, and our second compound in development, pamrevlumab.

To date, we have invested a substantial portion of our efforts and financial resources in the research and development of roxadustat, which is currently our lead product candidate. Roxadustat is our only product candidate that has advanced into a potentially pivotal trial, and it may be years before the studies required for its approval are completed, if ever. Our other product candidates are less advanced in development and may never enter into pivotal studies. We have completed 26 Phase 1 and 2 clinical studies with roxadustat in North America, Europe and Asia, in which more than 1,400 subjects have participated and for which we reported favorable primary and secondary safety and efficacy endpoint results. Based on our discussions with regulatory authorities, we believe that we have an acceptable plan for the conduct of our Phase 3 clinical programs to support NDA submissions in the U.S. and China. We have discussed our Phase 3 clinical development program with three national health authorities in the EU and obtained scientific advice from the European Medicines Agency. Our near-term prospects, including maintaining our existing collaborations with Astellas and AstraZeneca, will depend heavily on successful Phase 3 development and commercialization of roxadustat.

Our other lead product candidate, pamrevlumab, is currently in clinical development for IPF, pancreatic cancer and DMD. Pamrevlumab requires substantial further development and investment. We do not have a collaboration partner for support of this compound, and, while we have promising open-label safety data and potential signals of efficacy, we would need to complete larger and more extensive controlled clinical trials to validate the results to date in order to continue further development of this product candidate. In addition, although there are many potentially promising indications beyond IPF, pancreatic cancer and DMD, we are still exploring indications for which further development of, and investment for, pamrevlumab may be appropriate. Accordingly, the costs and time to complete development and related risks are currently unknown. Moreover, pamrevlumab is a monoclonal antibody, which may require experience and expertise that we may not currently possess as well as financial resources that are potentially greater than those required for our small molecule lead compound, roxadustat.

The clinical and commercial success of roxadustat and pamrevlumab will depend on a number of factors, many of which are beyond our control, and we may be unable to complete the development or commercialization of roxadustat or pamrevlumab.

The clinical and commercial success of roxadustat and pamrevlumab will depend on a number of factors, including the following:

- the timely initiation, continuation and completion of our Phase 3 clinical trials for roxadustat, which will depend substantially upon requirements for such trials imposed by the U.S. Food and Drug Administration ("FDA") and other regulatory agencies and bodies and the continued commitment and coordinated and timely performance by our third party collaboration partners, AstraZeneca and Astellas;
- the timely initiation and completion of our Phase 2 clinical trials for pamrevlumab, including in IPF, pancreatic cancer, and DMD;
- our ability to demonstrate the safety and efficacy of our product candidates to the satisfaction of the relevant regulatory authorities;
- whether we are required by the FDA or other regulatory authorities to conduct additional clinical trials, and the scope and nature of such clinical trials, prior to approval to market our products;
- the timely receipt of necessary marketing approvals from the FDA and foreign regulatory authorities, including pricing and reimbursement determinations:
- the ability to successfully commercialize our product candidates, if approved, for marketing and sale by the FDA or foreign regulatory authorities, whether alone or in collaboration with others;
- our ability and the ability of our third party manufacturing partners to manufacture quantities of our product candidates at quality levels necessary to meet regulatory requirements and at a scale sufficient to meet anticipated demand at a cost that allows us to achieve profitability;
- our success in educating health care providers and patients about the benefits, risks, administration and use of our product candidates, if approved:
- acceptance of our product candidates, if approved, as safe and effective by patients and the healthcare community;
- the success of efforts to enter into relationships with large dialysis organizations involving the administration of roxadustat to dialysis
- the achievement and maintenance of compliance with all regulatory requirements applicable to our product candidates;
- the maintenance of an acceptable safety profile of our products following any approval;

- the availability, perceived advantages, relative cost, relative safety, and relative efficacy of alternative and competitive treatments;
- our ability to obtain and sustain an adequate level of pricing or reimbursement for our products by third party payors;
- our ability to enforce successfully our intellectual property rights for our product candidates and against the products of potential competitors; and
- our ability to avoid or succeed in third party patent interference or patent infringement claims.

Many of these factors are beyond our control. Accordingly, we cannot assure you that we will ever be able to achieve profitability through the sale of, or royalties from, our product candidates. If we or our collaboration partners are not successful in obtaining approval for and commercializing our product candidates, or are delayed in completing those efforts, our business and operations would be adversely affected.

We may be unable to obtain regulatory approval for our product candidates, or such approval may be delayed or limited, due to a number of factors, many of which are beyond our control.

The clinical trials and the manufacturing of our product candidates are and will continue to be, and the marketing of our product candidates will be, subject to extensive and rigorous review and regulation by numerous government authorities in the U.S. and in other countries where we intend to develop and, if approved, market any product candidates. Before obtaining regulatory approval for the commercial sale of any product candidate, we must demonstrate through extensive preclinical trials and clinical trials that the product candidate is safe and effective for use in each indication for which approval is sought. The regulatory review and approval process is expensive and requires substantial resources and time, and in general very few product candidates that enter development receive regulatory approval. In addition, our collaboration partners for roxadustat have final control over development decisions in their respective territories and they may make decisions with respect to development or regulatory authorities that delay or limit the potential approval of roxadustat, or increase the cost of development or commercialization. Accordingly, we may be unable to successfully develop or commercialize roxadustat or pamrevlumab or any of our other product candidates.

We have not obtained regulatory approval for any of our product candidates and it is possible that roxadustat and pamrevlumab will never receive regulatory approval in any country. Regulatory authorities may take actions or impose requirements that delay, limit or deny approval of roxadustat or pamrevlumab for many reasons, including, among others:

- our failure to adequately demonstrate to the satisfaction of regulatory authorities that roxadustat is safe and effective in treating anemia in CKD or that pamrevlumab is safe and effective in treating IPF, pancreatic cancer, or DMD;
- our failure to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;
- the determination by regulatory authorities that additional clinical trials are necessary to demonstrate the safety and efficacy of roxadustat or pamrevlumab, or that ongoing clinical trials need to be modified in design, size, conduct or implementation;
- our product candidates may exhibit an unacceptable safety signal as they advance through clinical trials, in particular controlled Phase 3 trials:
- the clinical research organizations ("CROs") that conduct clinical trials on our behalf may take actions outside of our control that materially adversely impact our clinical trials;
- we or third party contractors manufacturing our product candidates may not maintain current good manufacturing practices ("cGMP"), successfully pass inspection or meet other applicable manufacturing regulatory requirements;
- regulatory authorities may not agree with our interpretation of the data from our preclinical trials and clinical trials;
- collaboration partners may not perform or complete their clinical programs in a timely manner, or at all; or
- principal investigators may determine that one or more serious adverse events ("SAEs"), is related or possibly related to roxadustat, and any such determination may adversely affect our ability to obtain regulatory approval, whether or not the determination is correct.

Any of these factors, many of which are beyond our control, could jeopardize our or our collaboration partners' abilities to obtain regulatory approval for and successfully market roxadustat. Because our business and operations in the near-term are almost entirely dependent upon roxadustat, any significant delays or impediments to regulatory approval could have a material adverse effect on our business and prospects.

Furthermore, in both the U.S. and China, we also expect to be required to perform additional clinical trials in order to obtain approval or as a condition to maintaining approval due to post-marketing requirements. If the FDA requires a risk evaluation and mitigation strategy ("REMS"), for any of our product candidates if approved, the substantial cost and expense of complying with a REMS or other post-marketing requirements may limit our ability to successfully commercialize our product candidates.

Preclinical, Phase 1 and Phase 2 clinical trial results may not be indicative of the results that may be obtained in larger, controlled Phase 3 clinical trials required for approval.

Clinical development is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. Success in preclinical and early clinical trials, which are often highly variable and use small sample sizes, may not be predictive of similar results in humans or in larger, controlled clinical trials, and successful results from early or small clinical trials may not be replicated or show as favorable an outcome, even if successful.

We have conducted only a limited number of Phase 2 clinical trials with pamrevlumab. We have conducted a randomized placebo-controlled study in 103 IPF patients with substudies in 57 IPF patients comparing pamrevlumab to one of two standards of care, an open-label Phase 2 dose escalation study of pamrevlumab for IPF in 89 patients, a Phase 2 dose finding trial of pamrevlumab combined with gemcitabine plus erlotinib in 75 patients with pancreatic cancer and a randomized double-blind placebo controlled study for liver fibrosis in subjects with hepatitis B, and we are currently conducting an open-label randomized, active-control, neoadjuvant Phase 2 trial in pancreatic cancer combining pamrevlumab with nabpaclitaxel plus gemcitabine in 37 patients. We cannot be sure that the results we have received to date from these trials will be substantiated in double-blinded pivotal trials with larger numbers of patients, that larger trials will demonstrate the efficacy of pamrevlumab for these or other indications, or that safety issues will not be uncovered in further trials. In the Phase 2 clinical trial for IPF, we used quantitative high-resolution computed tomography ("quantitative HRCT"), to measure the extent of lung fibrosis. While we believe that quantitative HRCT is an accurate measure of lung fibrosis, it is a novel technology that has not yet been accepted by the FDA as a primary endpoint in pivotal clinical trials. In addition, while we believe that the limited animal and human studies conducted to date suggest that pamrevlumab has the potential to arrest or reverse fibrosis and reduce tumor mass in some patients or diseases, we cannot be sure that these results will be indicative of the effects of pamrevlumab in larger human trials. In addition, the IPF and pancreatic cancer patient populations are extremely ill and routinely experience SAEs, including death, which may be attributed to pamrevlumab in a manner that negatively impacts the safety profile of our product candidate. If the additional clinical trials that we are planning or are currently conducting for pamrevlumab do not show favorable efficacy results or result in safety concerns, or if we do not meet our clinical endpoints with statistical significance, or demonstrate an acceptable risk-benefit profile, we may be prevented from or delayed in obtaining marketing approval for pamrevlumab in one or both of these indications.

In the past we developed an earlier generation product candidate aimed at treating anemia in CKD that resulted in a clinical hold for a safety signal seen in that product in Phase 2 clinical trials. The clinical hold applied to that product candidate and roxadustat was lifted for both product candidates after submission of the requested information to the FDA. While we have not seen similar safety concerns involving roxadustat to date, our Phase 2 clinical trials have involved a relatively small number of patients exposed to roxadustat for a relatively short period of time compared to the Phase 3 clinical trials that we are conducting, and only a fraction of the patients in the Phase 2 clinical trials were randomized to placebo. Accordingly, the Phase 2 clinical trials that we have conducted may not have uncovered safety issues, even if they exist. Some of the safety concerns associated with the treatment of patients with anemia in CKD using erythropoiesis stimulating agents ("ESAs") did not emerge for many years until placebo-controlled studies had been conducted in large numbers of patients. And while the data monitoring committee for our global Phase 3 anemia trials has consistently determined that our trials should continue without modification to the protocol, safety issues may still be discovered upon review of unblinded data when studies are completed. The biochemical pathways that we believe are affected by roxadustat are implicated in a variety of biological processes and disease conditions, and it is possible that the use of roxadustat to treat larger numbers of patients will demonstrate unanticipated adverse effects, including possible drug interactions, which may negatively impact the safety profile, use and market acceptance of roxadustat. We studied the potential interaction between roxadustat and three statins (atorvastatin, rosuvastatin, and simvastatin), which are used to lower levels of lipids in the blood. An adverse effect associated with increased statin plasma concentration is myopathy, which typically presents in a form of myalgia. The studies indicated the potential for increased exposure to those statins when roxadustat is taken simultaneously with those statins and suggested the need for statin dose reductions for patients receiving higher statin doses. We performed additional clinical pharmacology studies to evaluate if the effect of any such interaction could be minimized or eliminated by a modification of the dosing schedule that would separate the administration of roxadustat and the statin, however, such studies showed no minimization of effect. It is possible that the potential for interaction between roxadustat and statins could lead to label provisions for statins or roxadustat relating, for example, to dose scheduling or recommended statin dose limitations. In CKD patients, statin therapy is often initiated earlier than treatment for anemia, and risks of myopathy have been shown to decrease with increased time on drug. While we believe the prior statin treatment history of such patients at established doses may reduce the risk of adverse effects from any interaction with roxadustat and facilitate any appropriate dose adjustments, we cannot be sure that this will be the case.

Our Phase 3 trials include a major adverse cardiac event ("MACE") safety endpoint, which is a composite endpoint designed to identify major safety concerns, in particular relating to cardiovascular events such as cardiovascular death, myocardial infarction and stroke. In addition, we expect that our Phase 3 clinical trials supporting approval in Europe will be required to include MACE+ as a safety endpoint which, in addition to the MACE endpoints, also incorporates measurements of hospitalization rates due to heart failure or unstable angina. As a result, our ongoing Phase 3 clinical trials may identify unanticipated safety concerns in the patient population under study. The FDA has also informed us that the MACE endpoint will need to be evaluated separately for our Phase 3 trials in non-dialysis dependent ("NDD")-CKD patients and our Phase 3 trials in dialysis dependent ("DD")-CKD patients. The MACE endpoint will be evaluated in pooled analysis across Phase 3 studies of similar study populations and requires demonstration of non-inferiority relative to comparator, which means that the MACE event rate in roxadustat-treated patients must have less than a specified probability of exceeding the rate in the comparator trial by a specified hazard ratio. The number of patients necessary in order to permit a statistical analysis with adequate ability to detect the relative risk of MACE or MACE+ events in different arms of the trial, referred to as statistical power, depends on a number of factors, including the rate at which MACE or MACE+ events occur per patient-year in the trial, treatment duration of the patients, the required hazard ratio, and the required statistical power and confidence intervals.

In addition, we cannot be sure that the potential advantages we believe roxadustat may have for treatment of patients with anemia in CKD, as compared to the use of ESAs, will be substantiated by our larger U.S. and European Phase 3 clinical trials, or that we will be able to include a discussion of such advantages in our labeling should we obtain approval. We believe that roxadustat may have certain benefits as compared to ESAs based on the data from our Phase 2 clinical trials and China Phase 3 trials conducted to date, including safety benefits, the absence of a hypertensive effect, the potential to lower cholesterol levels and the potential to correct anemia without the use of IV iron. However, our belief that roxadustat may offer those benefits is based on a limited amount of data from our clinical trials to date, and our understanding of the likely mechanisms of action for roxadustat. Some of these benefits, such as those associated with the apparent effects on blood pressure and cholesterol, are not fully understood and, even if roxadustat receives marketing approval, we do not expect that it will be approved for the treatment of high blood pressure or high cholesterol based on the data from our Phase 3 trials, and we may not be able to refer to any such benefits in the labeling. While the data from our Phase 2 trials suggests roxadustat may reduce low-density lipoprotein ("LDL"), and reduce the ratio of LDL to high-density lipoprotein ("HDL"), the data show it may also reduce HDL, which may be a risk to patients. In addition, causes of the safety concerns associated with the use of ESAs to achieve specified target Hb levels have not been fully elucidated. While we believe that the issues giving rise to these concerns with ESAs are likely due to factors other than the Hb levels achieved, we cannot be certain that roxadustat will not be associated with similar, or more severe, safety concerns.

Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials after achieving positive results in early-stage development, and we may face similar setbacks. In addition, the CKD patient population has many afflictions that may cause severe illness or death, which may be attributed to roxadustat in a manner that negatively impacts the safety profile of our product candidate. If the results of our ongoing or future clinical trials for roxadustat are inconclusive with respect to efficacy, if we do not meet our clinical endpoints with statistical significance, or if there are unanticipated safety concerns or adverse events that emerge during clinical trials, we may be prevented from or delayed in obtaining marketing approval for roxadustat, and even if we obtain marketing approval, any sales of roxadustat may suffer.

We do not know whether our ongoing or planned Phase 3 clinical trials in roxadustat or Phase 2 clinical trials in pamrevlumab will need to be redesigned based on interim results, be able to achieve sufficient enrollment or be completed on schedule, if at all.

Clinical trials can be delayed or terminated for a variety of reasons, including delay or failure to:

- address any physician or patient safety concerns that arise during the course of the trial;
- obtain required regulatory or institutional review board ("IRB") approval or guidance;
- reach timely agreement on acceptable terms with prospective CROs and clinical trial sites;
- recruit, enroll and retain patients through the completion of the trial;
- maintain clinical sites in compliance with clinical trial protocols;
- initiate or add a sufficient number of clinical trial sites; and
- manufacture sufficient quantities of product candidate for use in clinical trials.

In addition, we could encounter delays if a clinical trial is suspended or terminated by us, by the relevant IRBs at the sites at which such trials are being conducted, or by the FDA or other regulatory authorities. A suspension or termination of clinical trials may result from any number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, changes in laws or regulations, or a principal investigator's determination that a serious adverse event could be related to our product candidates. Any delays in completing our clinical trials will increase the costs of the trial, delay the product candidate development and approval process and jeopardize our ability to commence marketing and generate revenues. Any of these occurrences may materially and adversely harm our business and operations and prospects.

Our product candidates may cause or have attributed to them undesirable side effects or have other properties that delay or prevent their regulatory approval or limit their commercial potential.

Undesirable side effects caused by our product candidates or that may be identified as related to our product candidates by physician investigators conducting our clinical trials or even competing products in development that utilize a similar mechanism of action or act through a similar biological disease pathway could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in the delay or denial of regulatory approval by the FDA or other regulatory authorities and potential product liability claims. Adverse events and SAEs that emerge during treatment with our product candidates or other compounds acting through similar biological pathways may be deemed to be related to our product candidate and may result in:

- our Phase 3 clinical trial development plan becoming longer and more extensive;
- regulatory authorities increasing the data and information required to approve our product candidates and imposing other requirements; and
- our collaboration partners terminating our existing agreements.

The occurrence of any or all of these events may cause the development of our product candidates to be delayed or terminated, which could materially and adversely affect our business and prospects. Refer to "Business - Our Development Program for Roxadustat" and "Business - Pamrevlumab for the Treatment of Fibrosis and Cancer" for a discussion of the adverse events and SAEs that have emerged in clinical trials of roxadustat and pamrevlumab.

Clinical trials of our product candidates may not uncover all possible adverse effects that patients may experience.

Clinical trials are conducted in representative samples of the potential patient population, which may have significant variability. Clinical trials are by design based on a limited number of subjects and of limited duration for exposure to the product used to determine whether, on a potentially statistically significant basis, the planned safety and efficacy of any product candidate can be achieved. As with the results of any statistical sampling, we cannot be sure that all side effects of our product candidates may be uncovered, and it may be the case that only with a significantly larger number of patients exposed to the product candidate for a longer duration, may a more complete safety profile be identified. Further, even larger clinical trials may not identify rare serious adverse effects or the duration of such studies may not be sufficient to identify when those events may occur. There have been other products, including ESAs, for which safety concerns have been uncovered following approval by regulatory authorities. Such safety concerns have led to labeling changes or withdrawal of ESAs products from the market. While our most advanced product candidate is chemically unique from ESAs, it or any of our product candidates may be subject to similar risks. For example, roxadustat for use in anemia in CKD is being developed to address a very diverse patient population expected to have many serious health conditions at the time of administration of roxadustat, including diabetes, high blood pressure and declining kidney function.

To date we have not seen evidence of significant safety concerns with our product candidates currently in clinical trials, patients treated with our products, if approved, may experience adverse reactions and it is possible that the FDA or other regulatory authorities may ask for additional safety data as a condition of, or in connection with, our efforts to obtain approval of our product candidates. If safety problems occur or are identified after our product candidates reach the market, we may, or regulatory authorities may require us to amend the labeling of our products, recall our products or even withdraw approval for our products.

We may fail to enroll a sufficient number of patients in our clinical trials in a timely manner, which could delay or prevent clinical trials of our product candidates.

Identifying and qualifying patients to participate in clinical trials of our product candidates is critical to our success. The timing of our clinical trials depends on the rate at which we can recruit and enroll patients in testing our product candidates. Patients may be unwilling to participate in clinical trials of our product candidates for a variety of reasons, some of which may be beyond our control:

- severity of the disease under investigation;
- availability of alternative treatments;
- size and nature of the patient population;
- eligibility criteria for and design of the study in question;
- perceived risks and benefits of the product candidate under study;
- ongoing clinical trials of competitive agents;
- physicians' and patients' perceptions of the potential advantages of our product candidates being studied in relation to available therapies or other products under development;
- our CRO's and our trial sites' efforts to facilitate timely enrollment in clinical trials;
- patient referral practices of physicians; and
- ability to monitor patients and collect patient data adequately during and after treatment.

Patients may be unwilling to participate in our clinical trials for roxadustat due to adverse events observed in other drug treatments of anemia in CKD, and patients currently controlling their disease with existing ESAs may be reluctant to participate in a clinical trial with an investigational drug. We may not be able to successfully initiate or continue clinical trials if we cannot rapidly enroll a sufficient number of eligible patients to participate in the clinical trials required by regulatory agencies. If we have difficulty enrolling a sufficient number of patients to conduct our clinical trials as planned, we may need to delay, limit or terminate on-going or planned clinical trials, any of which could have a material and adverse effect on our business and prospects.

If we or third party manufacturers on which we rely cannot manufacture sufficient quantities of our product candidates, or at sufficient quality, we may experience delays in development, regulatory approval, launch or commercialization.

Completion of our clinical trials and commercialization of our product candidates require access to, or development of, facilities to manufacture our product candidates at sufficient yields and at commercial scale. We have not yet entered into any commercial supply agreements with third-party manufacturers. We have limited experience manufacturing, or managing third parties in manufacturing any of our product candidates in the volumes that are expected to be necessary to support large-scale clinical trials and sales. In addition, we have limited experience forecasting or coordinating forecasting supply for launch or commercialization, which is a complex process involving our third-party manufacturers and for roxadustat our collaboration partners. We may not be able to sufficiently forecast supplies for commercial launch, or do so in a timely manner and our efforts to establish these manufacturing capabilities may not meet our requirements as to quantities, scale-up, yield, cost, potency or quality in compliance with cGMP.

We have a limited amount of roxadustat and pamrevlumab in storage, limited capacity reserved at our third-party manufacturers, and there are long lead times required to manufacture and scale-up the manufacture of additional supply, as required for both late-stage clinical trials and commercial supply. If we are unable to forecast, order or manufacture sufficient quantities of roxadustat or pamrevlumab on a timely basis, it may delay our development, launch or commercialization in some or all indications we are currently pursuing. For example, prior to agreement with regulatory authorities on the scope of our Phase 3 IPF trial design, there is uncertainty as to whether our supply plans will meet our clinical requirements in a timely manner. Any delay or interruption in the supply of our product candidates or products could have a material adverse effect on our business and operations.

Our clinical trials must be conducted with product produced under applicable cGMP regulations. Failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. We and even an experienced third party manufacturer may encounter difficulties in production, which difficulties may include:

- costs and challenges associated with scale-up and attaining sufficient manufacturing yields, in particular for biologic products such as pamrevlumab, which is a monoclonal antibody;
- · supply chain issues, including coordination of multiple contractors in our supply chain;
- the timely availability and shelf life requirements of raw materials and supplies;

- quality control and assurance;
- shortages of qualified personnel and capital required to manufacture large quantities of product;
- compliance with regulatory requirements that vary in each country where a product might be sold;
- capacity or forecasting limitations and scheduling availability in contracted facilities; and
- natural disasters, such as floods, storms, earthquakes, tsunamis, and droughts, or accidents such as fire, that affect facilities, possibly
 limit or postpone production, and increase costs.

Even if we are able to obtain regulatory approval of our product candidates, the label we obtain may limit the indicated uses for which our product candidates may be marketed.

With respect to roxadustat, we expect that regulatory approvals, if obtained at all, will limit the approved indicated uses for which roxadustat may be marketed, as ESAs have been subject to significant safety limitations on usage as directed by the "Black Box" warnings included in their labels. Refer to "Business - Roxadustat for the Treatment of Anemia in Chronic Kidney Disease - Limitations of the Current Standard of Care for Anemia in CKD". In addition, in the past, an approved ESA was voluntarily withdrawn due to serious safety issues discovered after approval. The safety concerns relating to ESAs may result in labeling for roxadustat containing similar warnings even if our Phase 3 clinical trials do not suggest that roxadustat has similar safety issues. Even if the label for roxadustat does not contain all of the warnings contained in the Black Box warning for ESAs, the label for roxadustat may contain other warnings that limit the market opportunity for roxadustat. These warnings could include warnings against exceeding specified Hb targets and other warnings that derive from the lack of clarity regarding the basis for the safety issues associated with ESAs, even if our Phase 3 clinical trials do not themselves raise safety concerns.

As an organization, we have never completed a Phase 3 clinical trial or received approval for a New Drug Application ("NDA") before, and may be unable to do so efficiently or at all for roxadustat or any product candidate we are developing.

We are currently conducting Phase 2 clinical trials for pamrevlumab and plan on initiating Phase 3 clinical trials for pamrevlumab in the future. We have initiated Phase 3 clinical trials of roxadustat. The conduct of Phase 3 clinical trials and the submission of a successful NDA is a complicated process. As an organization, we have not completed a Phase 3 clinical trial before, have limited experience in preparing, submitting and prosecuting regulatory filings, and have not received approval for an NDA before. Consequently, we may be unable to successfully and efficiently execute and complete necessary clinical trials in a way that leads to NDA submission and approval of roxadustat or for any other product candidate we are developing, even if our earlier stage clinical trials are successful. We may require more time and incur greater costs than our competitors and may not succeed in obtaining regulatory approvals of product candidates that we develop. Failure to commence or complete, or delays in, our planned clinical trials would prevent us from or delay us in commercializing roxadustat or any other product candidate we are developing.

In addition, in order for any Phase 3 clinical trial to support an NDA submission for approval, the FDA and foreign regulatory authorities require compliance with regulations and standards, including good clinical practices ("GCP") requirements for designing, conducting, monitoring, recording, analyzing and reporting the results of clinical trials to ensure that the data and results from trials are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. Although we rely on third parties to conduct our clinical trials, we as the sponsor remain responsible for ensuring that each of these clinical trials is conducted in accordance with its general investigational plan and protocol under legal and regulatory requirements, including GCP. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of our CROs, trial sites, principal investigators or other third parties fail to comply with applicable GCP requirements, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or other regulatory authorities may require us to exclude the use of patient data from our clinical trials not conducted in compliance with GCP or perform additional clinical trials before approving our marketing applications. They may even reject our application for approval or refuse to accept our future applications for an extended time period. For example in China, the China Food and Drug Administration ("CFDA") issued guidance in March 2016 related to its clinical trial data integrity regulations. While trial sites and CROs bear liability for the accuracy and authenticity of data they are directly responsible for, the sponsor ultimately bears full responsibility for submitted clinical data and the drug application dossier. Fraudulent clinical data could result in a ban in China of a sponsor's product-related NDA applications for three years and other NDA applications for one year. We have taken extensive steps to ensure the integrity of our China clinical data. However, we cannot assure you that upon inspection by a regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP requirements or that our results will be deemed authentic or may be used in support of our regulatory submissions.

If we are unable to establish sales, marketing and distribution capabilities or enter into or maintain agreements with third parties to market and sell our product candidates, we may not be successful in commercializing our product candidates if and when they are approved.

We do not have a sales or marketing infrastructure and have no experience in the sales, marketing or distribution of pharmaceutical products in any country. To achieve commercial success for any product for which we obtain marketing approval, we will need to establish sales and marketing capabilities or make and maintain our existing arrangements with third parties to perform these services at a level sufficient to support our commercialization efforts

To the extent that we would undertake sales and marketing of any of our products directly, there are risks involved with establishing our own sales, marketing and distribution capabilities. Factors that may inhibit our efforts to commercialize our products on our own include:

- our inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future products;
- our inability to effectively manage geographically dispersed sales and marketing teams;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- · unforeseen costs and expenses associated with creating an independent sales and marketing organization.

With respect to roxadustat, we are dependent on the commercialization capabilities of our collaboration partners, AstraZeneca and Astellas. If either such partner were to terminate its agreement with us, we would have to commercialize on our own or with another third party. We will have limited or little control over the commercialization efforts of such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products, if any, effectively. If they are not successful in commercializing our product candidates, our business and financial condition would suffer.

We face substantial competition, which may result in others discovering, developing or commercializing products before, or more successfully, than we do.

The development and commercialization of new pharmaceutical products is highly competitive. Our future success depends on our ability to achieve and maintain a competitive advantage with respect to the development and commercialization of our product candidates. Our objective is to discover, develop and commercialize new products with superior efficacy, convenience, tolerability and safety. We expect that in many cases, the products that we commercialize will compete with existing, market-leading products of companies that have large, established commercial organizations.

If roxadustat is approved and launched commercially, competing drugs are expected to include ESAs, particularly in those patient segments where ESAs are used. Currently available ESAs include epoetin alfa (EPOGEN ®, marketed by Amgen Inc. in the U.S., Procrit ® and Erypo ®/Eprex ®, marketed by Johnson & Johnson Inc., and Espo ® marketed by Kyowa Hakko Kirin in Japan and China), darbepoetin (Amgen/Kyowa Hakko Kirin's Aranesp ® and NESP ®) and Mircera ® marketed by Hoffmann-La Roche ("Roche") outside of the U.S. and by Vifor Pharma (formerly a company of Galenica Group ("Vifor")), a Roche licensee, in the U.S. and Puerto Rico, as well as biosimilar versions of these currently marketed ESA products. ESAs have been used in the treatment of anemia in CKD for more than 20 years, serving a significant majority of DD-CKD patients. While NDD-CKD patients who are not under the care of nephrologists, including those with diabetes and hypertension, do not typically receive ESAs and are often left untreated, some patients under nephrology care may be receiving ESA therapy. It may be difficult to encourage healthcare providers and patients to switch to roxadustat from products with which they have become familiar.

We may also face competition from potential new anemia therapies currently in clinical development, including in those patient segments not currently addressed by ESAs. Companies such as GlaxoSmithKline plc ("GSK"), Bayer Corporation ("Bayer"), Akebia Therapeutics, Inc. ("Akebia"), and Japan Tobacco, who are currently developing HIF prolyl hydroxylase ("HIF-PH") inhibitors for anemia in CKD indications. We may face competition for patient recruitment and enrollment for clinical trials and potentially in commercial sales. Akebia is currently conducting two Phase 3 studies in NDD-CKD, one started in December 2015 and the other in February 2016, and initiated two Phase 3 studies in DD-CKD, one started in July 2016 and the other in August 2016. Akebia also started a Phase 2 study in May 2017 with 20-week dosing initially in ESA-hyporesponsive DD-CKD patients but recently announced that is now modified to include non-hyporesponsive DD-CKD patients. More recently, Akebia announced an updated plan for a Phase 3 study with three-times a week dosing versus once a day dosing in DD-CKD population, which is expected to start in 2018. In September 2017, Mitsubishi Tanabe Pharmaceutical Corporation, Akebia's collaboration partner, announced topline results from a vadadustat Japan Phase 2 study in 51 NDD patients, and its plan to start a Japan Phase 3 development program, rather than including Japan sites in their global Phase 3 program. GSK started Phase 3 studies in NDD-CKD and DD-CKD in the U.S. in September 2016, and in Japan in June 2016. Bayer has completed global Phase 2 studies and announced in May 2017 its HIF-PH inhibitor is now in continued development in Japan only, and started Japan Phase 3 studies in NDD-CKD and DD-CKD in December 2017. Beginning in September 2017, Japan Tobacco is currently conducting four Phase 3 open label studies in NDD-CKD and DD-CKD in Japan. Some of these product candidates may enter the market prior to roxadustat.

In addition, there are other companies developing biologic therapies for the treatment of other anemia indications that we may also seek to pursue in the future, including anemia of myelodysplastic syndromes ("MDS"), for which we received approval from the CFDA for our Phase 2/3 clinical trial application in China and acceptance of our Investigational New Drug Application ("IND") and the Phase 3 pivotal study protocol from the FDA, and expect to start additional studies in the first half of 2018. For example, Acceleron Pharma Inc., in partnership with Celgene Corporation, is in Phase 3 development of protein therapeutic candidates to treat anemia and associated complications in patients with β-thalassemia and MDS, and has received orphan drug status from the EMA and FDA for these indications. There may also be new therapies for renal-related diseases that could limit the market or level of reimbursement available for roxadustat if and when it is commercialized.

In China, biosimilars of epoetin alfa are offered by Chinese pharmaceutical companies such as EPIAO marketed by 3SBio Inc. as well as more than 15 other local manufacturers. We may also face competition by HIF-PH inhibitors from other companies such as Akebia, Bayer, and GSK, which was authorized by the CFDA to conduct trials in China to support its ex-China regulatory filings. Akebia announced in December 2015 that it has entered into a development and commercialization partnership with Mitsubishi Tanabe Pharmaceutical Corporation for its HIF-PH inhibitor vadadustat in Japan, Taiwan, South Korea, India, and certain other countries in Asia, and announced in April 2017 an expansion of their U.S. collaboration with Otsuka to add markets, including China. 3SBio Inc. also announced in 2016 its plan on beginning a Phase 1 clinical trial of a HIF-PH inhibitor for the China market.

The introduction of biosimilar ESAs into the market in the U.S. may occur by the time roxadustat enters the market and may alter the competitive and pricing landscape of anemia therapy in DD-CKD patients under the end stage renal disease bundle. The patents for Amgen's epoetin alfa, EPOGEN, expired in 2004 in the European Union ("EU"), and the final material patents in the U.S. expired in May 2015. Several biosimilar versions of currently marketed ESAs are available for sale in the EU, China and other territories. In the U.S., a few ESA biosimilars are currently under development or regulatory review, including Retacrit® (epoetin zeta), marketed by Pfizer in Europe and for which Pfizer resubmitted a Biologics License Application ("BLA") after receiving a complete response letter ("CRL") from the FDA denying approval of its BLA submitted in October 2015. While FDA's Advisory Committee recommended approving the BLA in May 2017, FDA issued another CRL on June 22, 2017. Sandoz, a division of Novartis, markets Binocrit® (epoetin alfa) in Europe and plans to file a biosimilar BLA in 2017 in the U.S.

The majority of the current CKD anemia market focuses on dialysis patients, who visit dialysis centers on a regular basis, typically three-times a week, and anemia therapies are administered as part of the visit. Two of the largest operators of dialysis clinics in the U.S., DaVita Healthcare Partners Inc. ("DaVita") and Fresenius Medical Care AG & Co. KGaA ("Fresenius"), collectively provide dialysis care to approximately 70% of U.S. dialysis patients, and therefore have historically won long-term contracts including rebate terms with Amgen. DaVita recently entered into a new 6-year sourcing and supply agreement with Amgen effective through 2022. Fresenius' contract with Amgen expired in 2015, and Fresenius is now administering Mircera® in a significant portion of its U.S. dialysis patients since Mircera was made available by Vifor. Successful penetration of this market may require a significant agreement with Fresenius or DaVita on favorable terms and on a timely basis.

If pamrevlumab is approved and launched commercially to treat IPF, competing drugs are expected to include Roche's pirfenidone, which is approved for marketing in Europe, Canada, Japan and the U.S., and Boehringer Ingelheim Pharma GmbH & Co. KG's nintedanib which has been approved in the U.S. and EU. Nintedanib is also in development for non-small cell lung cancer and ovarian cancer. Other potential competitive product candidates in various stages of Phase 2 development for IPF include Promedior Inc.'s PRM-151, Biogen-Idec's STX-100, Prometic Life Sciences Inc.'s PBI-4050, and Kadmon Holdings, Inc.'s KD025.

If pamrevlumab is approved and launched commercially to treat pancreatic cancer, we expect it to be used in combination instead of as monotherapy, and, likely competition for pamrevlumab would be from other agents also seeking approval in combination with gemcitibine and nab-paclitaxel from companies such as NewLink Genetics Corporation, Merrimack Pharmaceuticals, Inc. ("Merrimack") and Halozyme Therapeutics, Inc. Gemcitabine and/or nab-paclitaxel are the current standard of care in the first-line treatment of metastatic pancreatic cancer. Celgene Corporation's Abraxane ® (nab-paclitaxel) was launched in the U.S. and Europe in 2013 and 2014, and was the first drug approved in this disease in nearly a decade. In 2015, Merrimack received FDA approval for the use of ONIVYDE (irinotecan liposome injection) for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

If pamrevlumab is approved and launched commercially to treat DMD, pamrevlumab may face competition for some patients from Sarepta Therapeutics, Inc. ("Sarepta"), as well as PTC Therapeutics, Santhera Pharmaceuticals, Catabasis Pharmaceuticals, Pfizer, Summit Therapeutics plc ("Summit") and Tivorsan Pharmaceuticals. Sarepta is researching and developing clinical candidates for many of the specific mutations in the dystrophin gene and recently received accelerated approval in the U.S. for its first drug Exondys 51 (eteplirsen). The approval is limited to patients who have a confirmed mutation in the DMD gene that is amenable to exon 51 skipping. This mutation represents a subset of approximately 13% of patients with DMD. Marathon Pharmaceuticals received approval for its drug Emflaza (deflazacort) on February 9, 2017 and on March 16, 2017 announced that it had sold the commercialization rights to Emflaza to PTC Therapeutics. PTC Therapeutics' product ataluren (Translarna TM) received conditional approval in Europe in 2014 and a complete response letter from the FDA in October of 2017 stating that the FDA is unable to approve the application in its current form. Translarna targets a different set of DMD patients from those being targeted by Sarepta's existing exonskipping therapeutic candidate; however it is also limited to a subset of patients who carry a specific mutation.

Conversely, pamrevlumab and some other potential competitors are intended to treat DMD patients regardless of the specific mutation. For example, Santhera Pharmaceuticals recently reported positive Phase 3 data with its drug idebenone (Raxone ®/Catena ®) in a trial measuring changes in lung function for DMD patients, however the FDA has asked for additional data from an ongoing trial prior to considering Raxone for approval. Previously we had expected this additional trial to be confirmatory rather than necessary for submission. Idebenone is a synthetic short-chain benzoquinone and a cofactor for the enzyme NAD(P)H:quinone oxidoreductase (NQO1). Pfizer's product candidate, which is in Phase 2 development to treat DMD, is an antibody targeting myostatin which is a protein that regulates muscle growth. The goal of the program is to increase muscle growth and muscle strength in patients with DMD. Summit and Tivorsan Pharmaceuticals are both working on drugs involving the utrophin pathway. Utrophin is a protein similar to dystrophin that is potentially implicated in all DMD patients. Summit is conducting a Phase 2 trial and reported positive interim data from this trial on January 25, 2018. Summit anticipates reporting topline data in the third quarter of 2018.

In October 2016, Summit and Sarepta announced a collaboration in which the companies have agreed to collaborate on Summit's utrophin modulator pipeline including its lead candidate ezutromid. The companies will co-develop the pipeline and Sarepta will receive the rights to the compounds in Europe, Turkey, and the Commonwealth of Independent States. Sarepta also has an option on the rights to the program for Latin America. Summit will retain commercialization rights in all other countries including the U.S.

Catabasis Pharmaceuticals recently reported positive Phase 2 data from its clinical trial candidate edasalonexent. Edasalonexent was reported to have preserved muscle function and slowed the progression of DMD compared to rates of change in the control period prior to treatment with edasalonexent. The company plans to start a placebo controlled Phase 3 trial in 2018.

If FG-5200 is approved and launched to treat corneal blindness resulting from partial thickness corneal damage without active inflammation and infection in China, it is likely to compete with other products designed to treat corneal damage. For example, in April 2015, a subsidiary of China Regenerative Medicine International Limited received approval for their acellular porcine cornea stroma medical device to treat patients in China with corneal ulcers and in April 2016, Guangzhou Yourvision Biotech Co. Ltd, a subsidiary of Guanhao Biotech, received approval for their acellular porcine cornea medical device to treat patients in China with infectious keratitis that does not respond to drug treatment.

The success of any or all of these potential competitive products may negatively impact the development and potential for success of pamrevlumab. In addition, any competitive products that are on the market or in development may compete with pamrevlumab for patient recruitment and enrollment for clinical trials or may force us to change our clinical trial comparators, whether placebo or active, in order to compare pamrevlumab against another drug, which may be the new standard of care.

Moreover, many of our competitors have significantly greater resources than we do. Large pharmaceutical companies, in particular, have extensive experience in clinical testing, obtaining regulatory approvals, recruiting patients, manufacturing pharmaceutical products, and commercialization. In the potential anemia market for roxadustat, for example, large and established companies such as Amgen and Roche, among others, compete aggressively to maintain their market shares. In particular, the currently marketed ESA products are supported by large pharmaceutical companies have greater experience and expertise in commercialization in the anemia market, including in securing reimbursement, government contracts and relationships with key opinion leaders; conducting testing and clinical trials; obtaining and maintaining regulatory approvals and distribution relationships to market products; and marketing approved products. These companies also have significantly greater scale research and marketing capabilities than we do and may also have products that have been approved or are in later stages of development, and have collaboration agreements in our target markets with leading dialysis companies and research institutions. These competitors have in the past successfully prevented new and competing products from entering into the anemia market, and we expect that their resources will represent challenges for us and our collaboration partners, AstraZeneca and Astellas. If we and our collaboration partners are not able to compete effectively against existing and potential competitors, our business and financial condition may be materially and adversely affected.

Our future commercial success depends upon attaining significant market acceptance of our product candidates, if approved, among physicians, patients, third party payors and others in the health care community.

Even if we obtain marketing approval for roxadustat, pamrevlumab or any other product candidates that we may develop or acquire in the future, these product candidates may not gain market acceptance among physicians, third party payors, patients and others in the health care community. Market acceptance of any approved product depends on a number of other factors, including:

- the clinical indications for which the product is approved and the labeling required by regulatory authorities for use with the product, including any warnings that may be required in the labeling;
- acceptance by physicians and patients of the product as a safe and effective treatment and the willingness of the target patient population to try new therapies and of physicians to prescribe new therapies;
- the cost, safety, efficacy and convenience of treatment in relation to alternative treatments;
- the restrictions on the use of our products together with other medications, if any;
- the availability of adequate coverage and reimbursement or pricing by third party payors and government authorities;
- the ability of treatment providers, such as dialysis clinics, to enter into relationships with us without violating their existing agreement;
- the effectiveness of our sales and marketing efforts.

No or limited reimbursement or insurance coverage of our approved products, if any, by third party payors may render our products less attractive to patients and healthcare providers.

Market acceptance and sales of any approved products will depend significantly on reimbursement or coverage of our products by the Chinese government or third party payors, and may be affected by existing and future healthcare reform measures or prices of related products for which the government or third party reimbursement applies. Coverage and reimbursement by the government or a third party payor may depend upon a number of factors, including the payor's determination that use of a product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- · cost-effective; and
- neither experimental nor investigational.

The cycle for the Chinese government to update their reimbursement lists (national or provincial) is unpredictable and is beyond the control of companies.

Obtaining coverage and reimbursement approval for a product from a government or other third party payor is a time consuming and costly process that could require us to provide supporting scientific, clinical and cost-effectiveness data for the use of our products to the payor, which we may not be able to provide. Furthermore, the reimbursement policies of third party payors may significantly change in a manner that renders our clinical data insufficient for adequate reimbursement or otherwise limits the successful marketing of our products. Even if we obtain coverage for our product candidates, third party payors may not establish adequate reimbursement amounts, which may reduce the demand for, or the price of, our products. If reimbursement is not available or is available only to limited levels, we may not be able to commercialize certain of our products.

Price controls may limit the price at which products such as roxadustat, if approved, are sold. For example, reference pricing is used by various EU member states and parallel distribution, or arbitrage between low-priced and high-priced member states, can further reduce prices. In some countries, we or our partner may be required to conduct a clinical trial or other studies that compare the cost-effectiveness of our product candidates to other available products in order to obtain or maintain reimbursement or pricing approval. Publication of discounts by third party payors or authorities may lead to further pressure on the prices or reimbursement levels within the country of publication and other countries. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unacceptable levels, we or our partner may elect not to commercialize our products in such countries, and our business and financial condition could be adversely affected.

Risks Related to Our Reliance on Third Parties

If our collaborations with Astellas or AstraZeneca were terminated, or if Astellas or AstraZeneca were to prioritize other initiatives over their collaborations with us, whether as a result of a change of control or otherwise, our ability to successfully develop and commercialize our lead product candidate, roxadustat, would suffer.

We have entered into collaboration agreements with respect to the development and commercialization of our lead product candidate, roxadustat, with Astellas and AstraZeneca. These agreements provide for reimbursement of our development costs by our collaboration partners and also provide for commercialization of roxadustat throughout the major territories of the world.

Our agreements with Astellas and AstraZeneca provide each of them with the right to terminate their respective agreements with us, upon the occurrence of negative clinical results, delays in the development and commercialization of our product candidates or adverse regulatory requirements or guidance. The termination of any of our collaboration agreements would require us to fund and perform the further development and commercialization of roxadustat in the affected territory, or pursue another collaboration, which we may be unable to do, either of which could have an adverse effect on our business and operations. In addition, each of those agreements provides our respective partners the right to terminate any of those agreements upon written notice for convenience. Moreover, if Astellas or AstraZeneca, or any successor entity, were to determine that their collaborations with us are no longer a strategic priority, or if either of them or a successor were to reduce their level of commitment to their collaborations with us, our ability to develop and commercialize roxadustat could suffer. In addition, some of our collaborations are exclusive and preclude us from entering into additional collaboration agreements with other parties in the area or field of exclusivity.

If we fail to establish and maintain strategic collaborations related to our product candidates, we will bear all of the risk and costs related to the development and commercialization of any such product candidate, and we may need to seek additional financing, hire additional employees and otherwise develop expertise at significant cost. This in turn may negatively affect the development of our other product candidates as we direct resources to our most advanced product candidates.

Conflicts with our collaboration partners could jeopardize our collaboration agreements and our ability to commercialize product candidates.

Our collaboration partners have certain rights to control decisions regarding the development and commercialization of our product candidates with respect to which they are providing funding. If we have a disagreement over strategy and activities, our plans for obtaining approval may be revised and negatively affect the anticipated timing and potential for success of our product candidates. Even if a product under a collaboration agreement is approved, we will remain substantially dependent on the commercialization strategy and efforts of our collaboration partners, and neither of our collaboration partners has experience in commercialization of a novel drug such as roxadustat in the dialysis market.

With respect to our collaboration agreements for roxadustat, there are additional complexities in that we and our collaboration partners, Astellas and AstraZeneca, must reach consensus on our Phase 3 development program. Multi-party decision-making is complex and involves significant time and effort, and there can be no assurance that the parties will cooperate or reach consensus, or that one or both of our partners will not ask to proceed independently in some or all of their respective territories or functional areas of responsibility in which the applicable collaboration partner would otherwise be obligated to cooperate with us. Any disputes or lack of cooperation with us by either Astellas or AstraZeneca may negatively impact the timing or success of our planned Phase 3 clinical studies.

We intend to conduct proprietary research programs in specific disease areas that are not covered by our collaboration agreements. Our pursuit of such opportunities could, however, result in conflicts with our collaboration partners in the event that any of our collaboration partners takes the position that our internal activities overlap with those areas that are exclusive to our collaboration agreements, and we should be precluded from such internal activities. Moreover, disagreements with our collaboration partners could develop over rights to our intellectual property. In addition, our collaboration agreements may have provisions that give rise to disputes regarding the rights and obligations of the parties. Any conflict with our collaboration partners could lead to the termination of our collaboration agreements, delay collaborative activities, reduce our ability to renew agreements or obtain future collaboration agreements or result in litigation or arbitration and would negatively impact our relationship with existing collaboration partners.

Certain of our collaboration partners could also become our competitors in the future. If our collaboration partners develop competing products, fail to obtain necessary regulatory approvals, terminate their agreements with us prematurely or fail to devote sufficient resources to the development and commercialization of our product candidates, the development and commercialization of our product candidates and products could be delayed.

We rely on third parties for the conduct of most of our preclinical and clinical trials for our product candidates, and if our third party contractors do not properly and successfully perform their obligations under our agreements with them, we may not be able to obtain or may be delayed in receiving regulatory approvals for our product candidates.

We rely heavily on university, hospital, dialysis centers and other institutions and third parties, including the principal investigators and their staff, to carry out our clinical trials in accordance with our clinical protocols and designs. We also rely on a number of third party CROs to assist in undertaking, managing, monitoring and executing our ongoing clinical trials, including those for roxadustat. We expect to continue to rely on CROs, clinical data management organizations, medical institutions and clinical investigators to conduct our development efforts in the future, including our Phase 3 development program for roxadustat. We compete with many other companies for the resources of these third parties, and large pharmaceutical companies often have significantly more extensive agreements and relationships with such third party providers, and such third party providers may prioritize the requirements of such large pharmaceutical companies over ours. The third parties on whom we rely may terminate their engagements with us at any time, which may cause delay in the development and commercialization of our product candidates. If any such third party terminates its engagement with us or fails to perform as agreed, we may be required to enter into alternative arrangements, which would result in significant cost and delay to our product development program. Moreover, our agreements with such third parties generally do not provide assurances regarding employee turnover and availability, which may cause interruptions in the research on our product candidates by such third parties.

Moreover, while our reliance on these third parties for certain development and management activities will reduce our control over these activities, it will not relieve us of our responsibilities. For example, the FDA and foreign regulatory authorities require compliance with regulations and standards, including GCP requirements for designing, conducting, monitoring, recording, analyzing and reporting the results of clinical trials to ensure that the data and results from trials are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. Although we rely on third parties to conduct our clinical trials, we, as the sponsor, remain responsible for ensuring that each of these clinical trials is conducted in accordance with its general investigational plan and protocol under legal and regulatory requirements, including GCP. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, principal investigators and trial sites.

If any of our CROs, trial sites, principal investigators or other third parties fail to comply with applicable GCP requirements, other regulations, trial protocol or other requirements under their agreements with us, the quality or accuracy of the data they obtain may be compromised or unreliable, and the trials of our product candidates may not meet regulatory requirements. If trials do not meet regulatory requirements or if these third parties need to be replaced, the development of our product candidates may be delayed, suspended or terminated, regulatory authorities may require us to exclude the use of patient data from our approval applications or perform additional clinical trials before approving our marketing applications. Regulatory authorities may even reject our application for approval or refuse to accept our future applications for an extended time period. We cannot assure you that upon inspection by a regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP requirements or that our results may be used in support of our regulatory submissions. If any of these events occur, we may not be able to obtain regulatory approval for our product candidates on a timely basis, at a reasonable cost, or at all.

We currently rely, and expect to continue to rely, on third parties to conduct many aspects of our clinical studies and product manufacturing, and these third parties may not perform satisfactorily.

We do not have any operating manufacturing facilities at this time other than our roxadustat and FG-5200 manufacturing facility in China, and our current commercial manufacturing facility plans in China are not expected to satisfy the requirements necessary to support development and commercialization outside of China. Other than in and for China specifically, we do not expect to independently manufacture our products. We currently rely, and expect to continue to rely, on third parties to scale-up, manufacture and supply roxadustat and our other product candidates outside of China. Risks arising from our reliance on third party manufacturers include:

- reduced control and additional burdens of oversight as a result of using third party manufacturers for all aspects of manufacturing activities, including regulatory compliance and quality control and assurance;
- termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that may negatively impact our planned development and commercialization activities;
- · the possible misappropriation of our proprietary technology, including our trade secrets and know-how; and
- disruptions to the operations of our third party manufacturers or suppliers unrelated to our product, including the bankruptcy of the manufacturer or supplier or a catastrophic event affecting our manufacturers or suppliers.

Any of these events could lead to development delays or failure to obtain regulatory approval, or affect our ability to successfully commercialize our product candidates. Some of these events could be the basis for action by the FDA or another regulatory authority, including injunction, recall, seizure or total or partial suspension of production.

The facilities used by our contract manufacturer to manufacture our product candidates must pass inspections by the FDA and other regulatory authorities. Although, except for China, we do not control the manufacturing operations of, and expect to remain completely dependent on, our contract manufacturers for manufacture of drug substance and finished drug product, we are ultimately responsible for ensuring that our product candidates are manufactured in compliance with cGMP requirements. If our contract manufacturers cannot successfully manufacture material that conforms to our or our collaboration partners' specifications, or the regulatory requirements of the FDA or other regulatory authorities, we may not be able to secure and/or maintain regulatory approval for our product candidates and our development or commercialization plans may be delayed. In addition, we have no control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. In addition, although our longer-term agreements are expected to provide for requirements to meet our quantity and quality requirements to manufacture our products candidates for clinical studies and commercial sale, we will have minimal direct control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel and we expect to rely on our audit rights to ensure that those qualifications are maintained to meet our requirements. If our contract manufacturers' facilities do not pass inspection by regulatory authorities, or if regulatory authorities do not approve these facilities for the manufacture of our products, or withdraw any such approval in the future, we would need to identify and qualify alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our products, if approved. Moreover, any failure of our third party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us or adverse regulatory consequences, including clinical holds, warnings or untitled letters, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which would be expected to significantly and adversely affect supplies of our products to us and our collaboration partners.

Any of our third party manufacturers may terminate their engagement with us at any time and we have not yet entered into any commercial supply agreements for the manufacture of active pharmaceutical ingredients ("APIs") or drug products. With respect to roxadustat, AstraZeneca and Astellas have certain rights to assume manufacturing of roxadustat and the existence of those rights may limit our ability to enter into favorable long-term supply agreements, if at all, with other third party manufacturers. In addition, our product candidates and any products that we may develop may compete with other product candidates and products for access and prioritization to manufacture. Certain third party manufacturers may be contractually prohibited from manufacturing our product due to non-compete agreements with our competitors or a commitment to grant another party priority relative to our products. There are a limited number of third party manufacturers that operate under cGMP and that might be capable of manufacturing to meet our requirements. Due to the limited number of third party manufacturers with the contractual freedom, expertise, required regulatory approvals and facilities to manufacture our products on a commercial scale, identifying and qualifying a replacement third party manufacturer would be expensive and time-consuming and may cause delay or interruptions in the production of our product candidates or products, which in turn may delay, prevent or impair our development and commercialization efforts.

We have a letter agreement with IRIX Pharmaceuticals, Inc. ("IRIX"), a third party manufacturer that we have used in the past, pursuant to which we agreed to negotiate a single source manufacturing agreement that included a right of first negotiation for the cGMP manufacture of HIF-PH inhibitors, including roxadustat, provided that IRIX is able to match any third party bids within 5%. The exclusive right to manufacture extends for five years after approval of an NDA for those compounds, and any agreement would provide that no minimum amounts would be specified until appropriate by forecast and that we and a commercialization partner would have the rights to contract with independent third parties that exceed IRIX's internal manufacturing capabilities or in the event that we or our commercialization partner determines for reasons of continuity of supply and security that such a need exists, provided that IRIX would supply no less than 65% of the product if it is able to provide this level of supply. Subsequent to the letter agreement, we and IRIX have entered into several additional service agreements. IRIX has requested in writing that we honor the letter agreement with respect to the single source manufacturing agreement, and if we were to enter into any such exclusive manufacturing agreement, there can be no assurance that IRIX will not assert a claim for right to manufacture roxadustat or that IRIX could manufacture roxadustat successfully and in accordance with applicable regulations for a commercial product and the specifications of our collaboration partners. In 2015, Patheon Pharmaceuticals Inc., a business unit of DPx Holdings B.V. ("Patheon"), acquired IRIX, and in 2017 ThermoFisher Scientific Inc. acquired Patheon.

If any third party manufacturer terminates its engagement with us or fails to perform as agreed, we may be required to find replacement manufacturers, which would result in significant cost and delay to our development programs. Although we believe that there are several potential alternative manufacturers who could manufacture our product candidates, we may incur significant delays and added costs in identifying, qualifying and contracting with any such third party or potential second source manufacturer. In any event, with any third party manufacturer we expect to enter into technical transfer agreements and share our know-how with the third party manufacturer, which can be time-consuming and may result in delays. These delays could result in a suspension or delay of our Phase 3 clinical trials or, if roxadustat is approved and marketed, a failure to satisfy patient demand.

Certain of the components of our product candidates are acquired from single-source suppliers and have been purchased without long-term supply agreements. The loss of any of these suppliers, or their failure to supply us with supplies of sufficient quantity and quality to complete our drug substance or finished drug product of acceptable quality and an acceptable price, would materially and adversely affect our business.

We do not have an alternative supplier of certain components of our product candidates. To date, we have used purchase orders for the supply of materials that we use in our product candidates. We may be unable to enter into long-term commercial supply arrangements with our vendors, or do so on commercially reasonable terms, which could have a material adverse impact upon our business. In addition, we currently rely on our contract manufacturers to purchase from third-party suppliers some of the materials necessary to produce our product candidates. We do not have direct control over the acquisition of those materials by our contract manufacturers. Moreover, we currently do not have any agreements for the commercial production of those materials.

The logistics of our supply chain, which include shipment of materials and intermediates from countries such as China and India add additional time and risk to the manufacture of our product candidates. While we have in the past maintained sufficient inventory of materials, API, and drug product to meet our and our collaboration partners' needs for roxadustat to date, the lead time and regulatory approvals required to source from and into countries outside of the U.S. increase the risk of delay and potential shortages of supply.

Risks Related to Our Intellectual Property

If our efforts to protect our proprietary technologies are not adequate, we may not be able to compete effectively in our market.

We rely upon a combination of patents, trade secret protection and contractual arrangements to protect the intellectual property related to our technologies. We will only be able to protect our products and proprietary information and technology by preventing unauthorized use by third parties to the extent that our patents, trade secrets, and contractual position allow us to do so. Any disclosure to or misappropriation by third parties of our trade secrets or confidential information could compromise our competitive position. Moreover, we are involved in, have in the past been involved in, and may in the future be involved in legal or administrative proceedings involving our intellectual property initiated by third parties, and which proceedings can result in significant costs and commitment of management time and attention. As our product candidates continue in development, third parties may attempt to challenge the validity and enforceability of our patents and proprietary information and technologies.

We also are involved in, have in the past been involved in, and may in the future be involved in initiating legal or administrative proceedings involving the product candidates and intellectual property of our competitors. These proceedings can result in significant costs and commitment of management time and attention, and there can be no assurance that our efforts would be successful in preventing or limiting the ability of our competitors to market competing products.

Composition-of-matter patents relating to the API are generally considered to be the strongest form of intellectual property protection for pharmaceutical products, as such patents provide protection not limited to any one method of use. Method-of-use patents protect the use of a product for the specified method(s), and do not prevent a competitor from making and marketing a product that is identical to our product for an indication that is outside the scope of the patented method. We rely on a combination of these and other types of patents to protect our product candidates, and there can be no assurance that our intellectual property will create and sustain the competitive position of our product candidates.

Biotechnology and pharmaceutical product patents involve highly complex legal and scientific questions and can be uncertain. Any patent applications that we own or license may fail to result in issued patents. Even if patents do successfully issue from our applications, third parties may challenge their validity or enforceability, which may result in such patents being narrowed, invalidated, or held unenforceable. Even if our patents and patent applications are not challenged by third parties, those patents and patent applications may not prevent others from designing around our claims and may not otherwise adequately protect our product candidates. If the breadth or strength of protection provided by the patents and patent applications we hold with respect to our product candidates is threatened, competitors with significantly greater resources could threaten our ability to commercialize our product candidates. Discoveries are generally published in the scientific literature well after their actual development, and patent applications in the U.S. and other countries are typically not published until 18 months after their filing, and in some cases are never published. Therefore, we cannot be certain that we or our licensors were the first to make the inventions claimed in our owned and licensed patents or patent applications, or that we or our licensors were the first to file for patent protection covering such inventions. Subject to meeting other requirements for patentability, for U.S. patent applications filed prior to March 16, 2013, the first to invent the claimed invention is entitled to receive patent protection for that invention while, outside the U.S., the first to file a patent application encompassing the invention is entitled to patent protection for the invention. The U.S. moved to a "first to file" system under the Leahy-Smith America Invents Act ("AIA"), effective March 16, 2013. This system also includes procedures for challenging issued patents and pending patent applications, which creates additional uncertainty. We may become involved in opposition or interference proceedings challenging our patents and patent applications or the patents and patent applications of others, and the outcome of any such proceedings are highly uncertain. An unfavorable outcome in any such proceedings could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology and compete directly with us, or result in our inability to manufacture, develop or commercialize our product candidates without infringing the patent rights of others.

In addition to the protection afforded by patents, we seek to rely on trade secret protection and confidentiality agreements to protect proprietary know-how, information, or technology that is not covered by our patents. Although our agreements require all of our employees to assign their inventions to us, and we require all of our employees, consultants, advisors and any third parties who have access to our trade secrets, proprietary know-how and other confidential information and technology to enter into appropriate confidentiality agreements, we cannot be certain that our trade secrets, proprietary know-how and other confidential information and technology will not be subject to unauthorized disclosure or that our competitors will not otherwise gain access to or independently develop substantially equivalent trade secrets, proprietary know-how and other information and technology. Furthermore, the laws of some foreign countries, in particular, China, where we have operations, do not protect proprietary rights to the same extent or in the same manner as the laws of the U.S. As a result, we may encounter significant problems in protecting and defending our intellectual property globally. If we are unable to prevent unauthorized disclosure of our intellectual property related to our product candidates and technology to third parties, we may not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business and operations.

Intellectual property disputes with third parties and competitors may be costly and time consuming, and may negatively affect our competitive position.

Our commercial success may depend on our avoiding infringement of the patents and other proprietary rights of third parties as well as on enforcing our patents and other proprietary rights against third parties. Pharmaceutical and biotechnology intellectual property disputes are characterized by complex, lengthy and expensive litigation over patents and other intellectual property rights. We may initiate or become party to, or be threatened with, future litigation or other proceedings regarding intellectual property rights with respect to our product candidates and competing products.

As our product candidates progress toward commercialization, we or our collaboration partners may be subject to patent infringement claims from third parties. We attempt to ensure that our product candidates do not infringe third party patents and other proprietary rights. However, the patent landscape in competitive product areas is highly complex, and there may be patents of third parties of which we are unaware that may result in claims of infringement. Accordingly, there can be no assurance that our product candidates do not infringe proprietary rights of third parties, and parties making claims against us may seek and obtain injunctive or other equitable relief, which could potentially block further efforts to develop and commercialize our product candidates including roxadustat or pamrevlumab. Any litigation involving defense against claims of infringement, regardless of the merit of such claims, would involve substantial litigation expense and would be a substantial diversion of management time.

We intend, if necessary, to vigorously enforce our intellectual property in order to protect the proprietary position of our product candidates, including roxadustat and pamrevlumab. Active efforts to enforce our patents may include litigation, administrative proceedings, or both, depending on the potential benefits that might be available from those actions and the costs associated with undertaking those efforts against third parties. We carefully review and monitor publicly available information regarding products that may be competitive with our product candidates and assert our intellectual property rights where appropriate. We previously prevailed in an administrative challenge initiated by a major biopharmaceutical company regarding our intellectual property rights, maintaining our intellectual property in all relevant scope, and will continue to protect and enforce our intellectual property rights. Moreover, third parties may continue to initiate new proceedings in the U.S. and foreign jurisdictions to challenge our patents from time to time.

We may consider administrative proceedings and other means for challenging third party patents and patent applications. Third parties may also challenge our patents and patent applications, through interference, reexamination, IPR, and post-grant review proceedings before the U.S. Patent and Trademark Office ("USPTO") or through other comparable proceedings, such as oppositions or invalidation proceedings, before foreign patent offices. An unfavorable outcome in any such challenge could require us to cease using the related technology and to attempt to license rights to it from the prevailing third party, which may not be available on commercially reasonable terms, if at all, in which case our business could be harmed. Even if we are successful, participation in administrative proceedings before the USPTO or a foreign patent office may result in substantial costs and time on the part of our management and other employees. For example, oppositions have been filed against four FibroGen European patents (European Patent Nos. 1463823, 1633333, 2322155, and 2322153) within our HIF Anemia-related Technologies Patent Portfolio.

Furthermore, there is a risk that any public announcements concerning the status or outcomes of intellectual property litigation or administrative proceedings may adversely affect the price of our stock. If securities analysts or our investors interpret such status or outcomes as negative or otherwise creating uncertainty, our common stock price may be adversely affected.

Our reliance on third parties and agreements with collaboration partners requires us to share our trade secrets, which increases the possibility that a competitor may discover them or that our trade secrets will be misappropriated or disclosed.

Our reliance on third party contractors to develop and manufacture our product candidates is based upon agreements that limit the rights of the third parties to use or disclose our confidential information, including our trade secrets and know-how. Despite the contractual provisions, the need to share trade secrets and other confidential information increases the risk that such trade secrets and information are disclosed or used, even if unintentionally, in violation of these agreements. In the highly competitive markets in which our product candidates are expected to compete, protecting our trade secrets, including our strategies for addressing competing products, is imperative, and any unauthorized use or disclosure could impair our competitive position and may have a material adverse effect on our business and operations.

In addition, our collaboration partners are larger, more complex organizations than ours, and the risk of inadvertent disclosure of our proprietary information may be increased despite their internal procedures and contractual obligations in place with our collaboration partners. Despite our efforts to protect our trade secrets and other confidential information, a competitor's discovery of such trade secrets and information could impair our competitive position and have an adverse impact on our business.

We have an extensive worldwide patent portfolio. The cost of maintaining our patent protection is high and maintaining our patent protection requires continuous review and compliance in order to maintain worldwide patent protection. We may not be able to effectively maintain our intellectual property position throughout the major markets of the world.

The USPTO and foreign patent authorities require maintenance fees and payments as well as continued compliance with a number of procedural and documentary requirements. Noncompliance may result in abandonment or lapse of the subject patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance may result in reduced royalty payments for lack of patent coverage in a particular jurisdiction from our collaboration partners or may result in competition, either of which could have a material adverse effect on our business.

We have made, and will continue to make, certain strategic decisions in balancing costs and the potential protection afforded by the patent laws of certain countries. As a result, we may not be able to prevent third parties from practicing our inventions in all countries throughout the world, or from selling or importing products made using our inventions in and into the U.S. or other countries. Third parties may use our technologies in territories in which we have not obtained patent protection to develop their own products and, further, may infringe our patents in territories which provide inadequate enforcement mechanisms, even if we have patent protection. Such third party products may compete with our product candidates, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

The laws of some foreign countries do not protect proprietary rights to the same extent as do the laws of the U.S., and we may encounter significant problems in securing and defending our intellectual property rights outside the U.S.

Many companies have encountered significant problems in protecting and defending intellectual property rights in certain countries. The legal systems of certain countries, particularly certain developing countries such as China, do not always favor the enforcement of patents, trade secrets, and other intellectual property rights, particularly those relating to pharmaceutical and biotechnology products, which could make it difficult for us to stop infringement of our patents, misappropriation of our trade secrets, or marketing of competing products in violation of our proprietary rights. In China, our intended establishment of significant operations will depend in substantial part on our ability to effectively enforce our intellectual property rights in that country. Proceedings to enforce our intellectual property rights in foreign countries could result in substantial costs and divert our efforts and attention from other aspects of our business, and could put our patents in these territories at risk of being invalidated or interpreted narrowly, or our patent applications at risk of not being granted, and could provoke third parties to assert claims against us. We may not prevail in all legal or other proceedings that we may initiate and, if we were to prevail, the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Intellectual property rights do not address all potential threats to any competitive advantage we may have.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations, and intellectual property rights may not adequately protect our business or permit us to maintain our competitive advantage. The following examples are illustrative:

- Others may be able to make compounds that are the same as or similar to our current or future product candidates but that are not covered by the claims of the patents that we own or have exclusively licensed.
- We or any of our licensors or strategic partners might not have been the first to make the inventions covered by the issued patent or pending patent application that we own or have exclusively licensed.
- We or any of our licensors or strategic partners might not have been the first to file patent applications covering certain of our inventions.
- Others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights.
- The prosecution of our pending patent applications may not result in granted patents.
- Granted patents that we own or have exclusively licensed may not provide us with any competitive advantages, or may be held invalid
 or unenforceable, as a result of legal challenges by our competitors.
- Patent protection on our product candidates may expire before we are able to develop and commercialize the product, or before we are able to recover our investment in the product.
- Our competitors might conduct research and development activities in the U.S. and other countries that provide a safe harbor from
 patent infringement claims for such activities, as well as in countries in which we do not have patent rights, and may then use the
 information learned from such activities to develop competitive products for sale in markets where we intend to market our product
 candidates.

The existence of counterfeit pharmaceutical products in pharmaceutical markets may compromise our brand and reputation and have a material adverse effect on our business, operations and prospects.

Counterfeit products, including counterfeit pharmaceutical products, are a significant problem, particularly in China. Counterfeit pharmaceuticals are products sold or used for research under the same or similar names, or similar mechanism of action or product class, but which are sold without proper licenses or approvals. Such products may be used for indications or purposes that are not recommended or approved or for which there is no data or inadequate data with regard to safety or efficacy. Such products divert sales from genuine products, often are of lower cost, often are of lower quality (having different ingredients or formulations, for example), and have the potential to damage the reputation for quality and effectiveness of the genuine product. If counterfeit pharmaceuticals illegally sold or used for research result in adverse events or side effects to consumers, we may be associated with any negative publicity resulting from such incidents. Consumers may buy counterfeit pharmaceuticals that are in direct competition with our pharmaceuticals, which could have an adverse impact on our revenues, business and results of operations. In addition, the use of counterfeit products could be used in non-clinical or clinical studies, or could otherwise produce undesirable side effects or adverse events that may be attributed to our products as well, which could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in the delay or denial of regulatory approval by the FDA or other regulatory authorities and potential product liability claims. With respect to China, although the government has recently been increasingly active in policing counterfeit pharmaceuticals, there is not yet an effective counterfeit pharmaceutical regulation control and enforcement system in China. As a result, we may not be able to prevent third parties from selling or purporting to sell our products in China. The proliferation of counterfeit pharmaceuticals has grown in recent years and may continue to grow in the future. The existence of and any increase in the sales and production of counterfeit pharmaceuticals, or the technological capabilities of counterfeiters, could negatively impact our revenues, brand reputation, business and results of operations.

Risks Related to Government Regulation

The regulatory approval process is highly uncertain and we may not obtain regulatory approval for the commercialization of our product candidates.

The time required to obtain approval by the FDA and comparable foreign regulatory authorities is unpredictable, but typically takes many years following the commencement of preclinical studies and clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions. We have not obtained regulatory approval for any product candidate, and it is possible that neither roxadustat nor pamrevlumab, nor any future product candidates we may discover, in-license or acquire and seek to develop in the future, will ever obtain regulatory approval.

Our product candidates could fail to receive regulatory approval from the FDA or other regulatory authorities for many reasons, including:

- disagreement over the design or implementation of our clinical trials;
- failure to demonstrate that a product candidate is safe and effective for its proposed indication;
- failure of clinical trials to meet the level of statistical significance required for approval;
- failure to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;
- disagreement over our interpretation of data from preclinical studies or clinical trials;
- disagreement over whether to accept efficacy results from clinical trial sites outside the U.S. where the standard of care is potentially different from that in the U.S.;
- the insufficiency of data collected from clinical trials of our present or future product candidates to support the submission and filing of an NDA or other submission or to obtain regulatory approval;
- disapproval of the manufacturing processes or facilities of either our manufacturing plant or third party manufacturers with whom we contract for clinical and commercial supplies; or
- changes in the approval policies or regulations that render our preclinical and clinical data insufficient for approval.

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The FDA or other regulatory authorities may require more information, including additional preclinical or clinical data to support approval, which may delay or prevent approval and our commercialization plans, or we may decide to abandon the development program altogether. Even if we do obtain regulatory approval, our product candidates may be approved for fewer or more limited indications than we request, approval may be contingent on the performance of costly post-marketing clinical trials, or approval may require labeling that does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate. In addition, if our product candidates produce undesirable side effects or safety issues, the FDA may require the establishment of REMS or other regulatory authorities may require the establishment of a similar strategy, that may, restrict distribution of our approved products, if any, and impose burdensome implementation requirements on us. Any of the foregoing scenarios could materially harm the commercial prospects for our product candidates.

Even if we believe our current or planned clinical trials are successful, regulatory authorities may not agree that our completed clinical trials provide adequate data on safety or efficacy. Approval by one regulatory authority does not ensure approval by any other regulatory authority. However, a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory process in others. We may not be able to file for regulatory approvals and even if we file we may not receive the necessary approvals to commercialize our product candidates in any market.

If our product candidates obtain marketing approval, we will be subject to more extensive healthcare laws, regulation and enforcement and our failure to comply with those laws could have a material adverse effect on our results of operations and financial condition.

If we obtain approval for any of our product candidates, the regulatory requirements applicable to our operations, in particular our sales and marketing efforts, will increase significantly with respect to our operations and the potential for civil and criminal enforcement by the federal government and the states and foreign governments will increase with respect to the conduct of our business. The laws that may affect our operations in the U.S. include:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving,
 offering or paying remuneration, directly or indirectly, to induce, or in return for, the purchase or recommendation of an item or service
 reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs;
- federal civil and criminal false claims laws and civil monetary penalty laws, which prohibit, among other things, individuals or entities
 from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third party payors that
 are false or fraudulent;
- the Health Insurance Portability and Accountability Act of 1996 ("HIPAA"), which created new federal criminal statutes that prohibit
 executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters;
- HIPAA, as amended by Health Information Technology and Clinical Health Act, and its implementing regulations, which imposes certain requirements relating to the privacy, security, and transmission of individually identifiable health information;
- the federal physician sunshine requirements under the Patient Protection and Affordable Care Act ("PPACA"), which requires manufacturers of drugs, devices, biologics, and medical supplies to report annually to the CMS, information related to payments and other transfers of value to physicians, other healthcare providers, and teaching hospitals, and ownership and investment interests held by physicians and other healthcare providers and their immediate family members;

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- foreign and state law equivalents of each of the above federal laws, such as the U.S. Foreign Corrupt Practices Act ("FCPA"), anti-kickback and false claims laws that may apply to items or services reimbursed by any third party payor, including commercial insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the applicable compliance guidance promulgated by the federal government, or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways, thus complicating compliance efforts; and
- the Trade Agreements Act ("TAA"), which requires that drugs sold to the U.S. Government must be manufactured in the U.S. or in TAA approved and designated countries. Drugs manufactured in countries not approved under the TAA, may not be sold to the U.S. without specific regulatory approval. We have little experience with this regulation and there is a risk that drugs made from Chinese-made API may not be sold to an entity of the U.S. such as the Veterans Health Administration ("VA") due to our inability to obtain regulatory approval. While there have been recent VA policy changes that appear to allow for sale of drugs from non-TAA approved countries, this policy may change or there may be additional policies or legislation that affect our ability to sell drug to the U.S. Government

The scope of these laws and our lack of experience in establishing the compliance programs necessary to comply with this complex and evolving regulatory environment increases the risks that we may violate the applicable laws and regulations. If our operations are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, the exclusion from participation in federal and state healthcare programs and imprisonment, any of which could materially adversely affect our ability to operate our business and our financial results.

The impact of recent U.S. healthcare reform, its potential partial or full repeal, and other changes in the healthcare industry and in healthcare spending is currently unknown, and may adversely affect our business model.

The commercial potential for our approved products, if any, could be affected by changes in healthcare spending and policy in the U.S. and abroad. We operate in a highly regulated industry and new laws, regulations or judicial decisions, or new interpretations of existing laws, regulations or decisions, related to healthcare availability, the method of delivery or payment for healthcare products and services could negatively impact our business, operations and financial condition.

In the U.S., the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 ("MMA") altered Medicare coverage and payments for pharmaceutical products. The legislation expanded Medicare coverage for drug purchases by the elderly and introduced a new reimbursement methodology based on average sales prices for physician-administered drugs. The MMA also provided authority for limiting the number of drugs that will be covered in any therapeutic class and as a result, we expect that there will be additional pressure to reduce costs. For example, the CMS in implementing the MMA has enacted regulations that reduced capitated payments to dialysis providers. These cost reduction initiatives and other provisions of the MMA could decrease the scope of coverage and the price that may be received for any approved dialysis products and could seriously harm our business and financial condition. While the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policies and payment limitations in setting their own reimbursement rates, and any reduction in reimbursement that results from the MMA may cause a similar reduction in payments from private payors. Similar regulations or reimbursement policies have been enacted in many international markets which could similarly impact the commercial potential for our products.

Under the Medicare Improvements for Patients and Providers Act ("MIPPA"), a basic case-mix adjusted composite, or bundled, payment system commenced in January 2011 and transitioned fully by January 2014 to a single reimbursement rate for drugs and all services furnished by renal dialysis centers for Medicare beneficiaries with end-stage renal disease. Specifically, under MIPPA the bundle now covers drugs, services, lab tests and supplies under a single treatment base rate for reimbursement by the Centers for Medicare and Medicaid Services ("CMS") based on the average cost per treatment, including the cost of ESAs and IV iron doses, typically without adjustment for usage. It is unknown whether roxadustat, if approved, will be included in the payment bundle. Under MIPPA, agents that have no IV equivalent in the bundle are currently expected to be excluded from the bundle until 2025. If roxadustat were included in the bundle, it may reduce the price that could be charged for roxadustat, and therefore potentially limit our profitability. Based on roxadustat's differentiated mechanism of action and therapeutic effects, and discussions with our collaboration partner, we currently believe that roxadustat might not be included in the bundle. If roxadustat is reimbursed outside of the bundle, it may potentially limit or delay market penetration of roxadustat.

More recently, the PPACA was enacted in 2010 with a goal of reducing the cost of healthcare and substantially changing the way healthcare is financed by both government and private insurers. The PPACA, among other things, increases the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extends the rebate program to individuals enrolled in Medicaid managed care organizations, establishes annual fees and taxes on manufacturers of certain branded prescription drugs, and creates a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D. In addition, other legislative changes have been proposed and adopted in the U.S. since the PPACA was enacted. On August 2, 2011, the Budget Control Act of 2011 created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least \$1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of up to 2% per fiscal year, which went into effect on April 1, 2013.

It is likely that federal and state legislatures within the U.S. and foreign governments will continue to consider changes to existing healthcare legislation. We cannot predict the reform initiatives that may be adopted in the future or whether initiatives that have been adopted will be repealed or modified. The continuing efforts of the government, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce costs of healthcare may adversely affect:

- the demand for any products that may be approved for sale;
- the price and profitability of our products;
- pricing, coverage and reimbursement applicable to our products;
- the ability to successfully position and market any approved product; and
- the taxes applicable to our pharmaceutical product revenues.

Some of the provisions of the PPACA have yet to be fully implemented, while certain provisions have been subject to judicial and Congressional challenges. In January 2017, Congress voted to adopt a budget resolution for fiscal year 2017, that while not a law, is widely viewed as the first step toward the passage of legislation that would repeal certain aspects of the PPACA. Further, on January 20, 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the Affordable Care Act to waive, defer, grant exemptions from, or delay the implementation of any provision of the Affordable Care Act that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. Congress also could consider subsequent legislation to replace elements of the Affordable Care Act that are repealed. Given these possibilities and others we may not anticipate, the full extent to which our business, results of operations and financial condition could be adversely affected by the recent proposed legislation and the Executive Order is uncertain. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our drugs.

Furthermore, legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot be sure whether additional legislative changes will be enacted, or whether FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the regulatory approvals of our product candidates, if any, may be. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent regulatory approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements.

We may not be able to conduct, or contract others to conduct, animal testing in the future, which could harm our research and development activities.

Certain laws and regulations relating to drug development require us to test our product candidates on animals before initiating clinical trials involving humans. Animal testing activities have been the subject of controversy and adverse publicity. Animal rights groups and other organizations and individuals have attempted to stop animal testing activities by pressing for legislation and regulation in these areas and by disrupting these activities through protests and other means. To the extent the activities of these groups are successful, our research and development activities may be interrupted or delayed.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could result in significant liability for us and harm our reputation.

We are exposed to the risk of employee fraud or other misconduct, including intentional failure to:

- comply with FDA regulations or similar regulations of comparable foreign regulatory authorities;
- provide accurate information to the FDA or comparable foreign regulatory authorities;
- comply with manufacturing standards we have established;
- comply with federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities;
- comply with the FCPA and other anti-bribery laws;
- report financial information or data accurately;
- or disclose unauthorized activities to us.

Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions, delays in clinical trials, or serious harm to our reputation. We have adopted a code of conduct for our directors, officers and employees, but it is not always possible to identify and deter employee misconduct. The precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could harm our business, results of operations, financial condition and cash flows, including through the imposition of significant fines or other sanctions.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could harm our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations applicable to our operations in the U.S. and foreign countries. These current or future laws and regulations may impair our research, development or manufacturing efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Risks Related to Our International Operations

We are establishing international operations and seeking approval to commercialize our product candidates outside of the U.S., in particular in China, and a number of risks associated with international operations could materially and adversely affect our business.

We expect to be subject to a number of risks related with our international operations, many of which may be beyond our control. These risks include:

- different regulatory requirements for drug approvals in foreign countries;
- different standards of care in various countries that could complicate the evaluation of our product candidates;
- different U.S. and foreign drug import and export rules;
- reduced protection for intellectual property rights in certain countries;
- unexpected changes in tariffs, trade barriers and regulatory requirements;

- different reimbursement systems and different competitive drugs indicated to treat the indications for which our product candidates are being developed;
- · economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- compliance with the FCPA, and other anti-corruption and anti-bribery laws;
- U.S. and foreign taxes, including withholding of payroll taxes;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country;
- workforce uncertainty in countries where labor unrest is more common than in the U.S.;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad;
- a reliance on CROs, clinical trial sites, principal investigators and other third parties that may be less experienced with clinical trials or have different methods of performing such clinical trials than we are used to in the U.S.;
- · potential liability resulting from development work conducted by foreign distributors; and
- business interruptions resulting from geopolitical actions, including war and terrorism, or natural disasters.

The pharmaceutical industry in China is highly regulated and such regulations are subject to change.

The pharmaceutical industry in China is subject to comprehensive government regulation and supervision, encompassing the approval, registration, manufacturing, packaging, licensing and marketing of new drugs. Refer to "Business - Government Regulation - Regulation in China" for a discussion of the regulatory requirements that are applicable to our current and planned business activities in China. In recent years, the regulatory framework in China regarding the pharmaceutical industry has undergone significant changes, and we expect that it will continue to undergo significant changes. Any such changes or amendments may result in increased compliance costs on our business or cause delays in or prevent the successful development or commercialization of our product candidates in China. Chinese authorities have become increasingly vigilant in enforcing laws in the pharmaceutical industry, in some cases launching industry-wide investigations, oftentimes appearing to focus on foreign companies. The costs and time necessary to respond to an investigation can be material. Any failure by us or our partners to maintain compliance with applicable laws and regulations or obtain and maintain required licenses and permits may result in the suspension or termination of our business activities in China.

Patients' use of traditional Chinese medicine in violation of study protocols in our China studies may lead the CFDA and regulators in other jurisdictions in which we are seeking approval to suspend our studies, reject our study data and withhold approval for roxadustat.

A common issue encountered in conducting clinical studies in China is patients' use of traditional Chinese medicine in violation of study protocols. We believe that many patients with anemia in CKD are currently being treated with traditional Chinese medicine, and it is possible that such patients may continue their use of traditional Chinese medicine after enrollment in our studies and in violation of study protocols. If the patients participating in our China clinical studies do not comply with study protocols and continue to use traditional Chinese medicine, adverse events may emerge in our studies that are due to such traditional Chinese medicine or the interaction between such traditional Chinese medicine and roxadustat. In addition, the use of traditional Chinese medicine by patients in our studies may confound our study results. The occurrence of such adverse events or the confounding of our study results may lead the CFDA and regulators in other jurisdictions in which we are seeking approval to, among other things, suspend our studies, reject our study data and withhold approval for roxadustat.

We are planning on using our own manufacturing facilities in China to produce roxadustat drug product, roxadustat API, and FG-5200 corneal implants. As an organization, we have limited experience in the construction, licensure, or operation of a manufacturing plant, and, accordingly we cannot assure you we will be able to meet regulatory requirements to operate our plant and to sell our products.

In 2014, we received a Pharmaceutical Production Permit ("PPP") for our facility in Beijing, and are currently building a manufacturing facility in Cangzhou, Hebei, in which we intend to manufacture roxadustat API for commercial use. The PPP allowed us to produce the NDA registration campaign of roxadustat in the Beijing facility according to cGMP. However, we will not receive a license for commercial manufacture of roxadustat in either facility until after NDA approval. For Cangzhou, we will first need to obtain a PPP and secure manufacturing site change approval. As an organization, we have limited experience building and licensing manufacturing facilities which must be constructed, licensed and operated in conformity with applicable cGMP, building and other requirements. There can be no assurance that we will be successful or timely in receiving licensure in Cangzhou or Beijing, either of which would be expected to delay or preclude our ability to develop and commercialize roxadustat in China and may materially adversely affect our business and operations and prospects in China.

We will be obligated to comply with continuing cGMP requirements and there can be no assurance that we will receive and maintain all of the appropriate licenses required to manufacture our product candidates for clinical and commercial use in China. In addition, we and our product suppliers must continually spend time, money and effort in production, record-keeping and quality assurance and appropriate controls in order to ensure that any products manufactured in our facilities meet applicable specifications and other requirements for product safety, efficacy and quality and there can be no assurance that our efforts will succeed for licensure or continue to be successful in meeting these requirements.

We would require separate approval for the manufacture of FG-5200. In addition, we may convert our existing manufacturing process of FG-5200 to a semi-automated process which may require us to show that implants from our new manufacturing process are comparable to the implants from our existing manufacturing process. There can be no assurance that we will successfully receive licensure and maintain approval for the manufacture of FG-5200, either of which would be expected to delay or preclude our ability to develop FG-5200 in China and may materially adversely affect our business and operations and prospects in China.

Manufacturing facilities in China are subject to periodic unannounced inspections by the CFDA and other regulatory authorities. We expect to depend on these facilities for our product candidates and business operations in China. Natural disasters or other unanticipated catastrophic events, including power interruptions, water shortages, storms, fires, earthquakes, terrorist attacks, government appropriation of our facilities, and wars, could significantly impair our ability to operate our manufacturing facilities. Certain equipment, records and other materials located in these facilities would be difficult to replace or would require substantial replacement lead time that would impact our ability to successfully commercialize our product candidates in China. The occurrence of any such event could materially and adversely affect our business, financial condition, results of operations, cash flows and prospects.

Our decision to seek approval in China for roxadustat prior to approval in the U.S. or Europe is largely unprecedented and could be subject to significant risk, delay and expense.

Our subsidiary FibroGen (China) Medical Technology Development Co., Ltd. ("FibroGen Beijing"), is currently seeking approval for roxadustat in China as a Domestic Class 1 Drug, which we believe, if approved, would be the first CFDA approval of a first in class drug candidate while Phase 3 trials are ongoing in the U.S. and Europe. Because of this largely novel regulatory pathway, the CFDA approval process may take longer than we currently expect, or the CFDA may require us to submit additional data including data from the U.S. or European Phase 3 trials. In addition, negative data from the U.S. or European Phase 3 trials could impact the CFDA approval process. Any such development delays would result in significant delay in our commercialization plans for roxadustat in China. Elements of our plan for approval of roxadustat and other product candidates in China are based on communications with the CFDA, some of which are not reflected in formal written communications, regulations, findings or determinations. Accordingly, while we believe we have understandings with the CFDA regarding the domestic drug approval process and the clinical and manufacturing (including bio-equivalency) data currently required for approval and the timing and process of a potential approval, the regulatory authorities may later determine that changes are required in the drug approval process, or that additional or different clinical or manufacturing data must be generated, any of which could significantly delay approval of roxadustat or any of our other product candidates, and materially and adversely affect our plans and operations in China. It is possible that other unforeseen delays in the China regulatory process could have a material adverse effect on our development and commercialization of roxadustat in China.

For example, prior to enrolling our Phase 3 studies, the Ministry of Science and Technology established a new approval process to obtain routine blood and urine samples that contain genetic information. Our Phase 3 CKD clinical trial sites have received such approval, but applications are reviewed only on a quarterly basis, thus new studies or work at additional clinical trial sites could be delayed until they receive such approval.

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In addition, there are new and evolving environmental and manufacturing regulations in China. The application thereof may impact our API manufacturing location or strategy. In order to prevent or mitigate any delay in commercialization, we are establishing a 5,500 square meter commercial API manufacturing facility in Cangzhou, Hebei, with the intention of being operational shortly after NDA approval. We have limited experience building and licensing manufacturing facilities which must be constructed, licensed and operated in conformity with applicable cGMP, building and other requirements. Any delays related to these regulations or our new manufacturing facility could adversely affect the cost timing of our commercialization in China.

In May 2016, China announced implementation of a three-year pilot program for the Marketing Authorization Holder System ("MAH") in certain piloted regions. We have applied to participate in this program, and if accepted, we may be able to outsource drug product or API manufacturing to third parties. However, we cannot know if we will be accepted into the MAH program, or how long such program will be available.

Even if roxadustat is approved in China, we and our collaboration partner in China, AstraZeneca, may experience difficulties in successfully generating sales of roxadustat in China.

We and AstraZeneca have a profit sharing arrangement with respect to roxadustat in China. Even if roxadustat is approved for sale in China, we and AstraZeneca may experience difficulties in our marketing, commercialization and sales efforts in China, and our business and operations could be adversely affected. In particular, sales of roxadustat in China may be limited due to the complex nature of the healthcare system, low average personal income, lack of patient cost reimbursement, pricing controls, poorly developed infrastructure and potentially rapid competition from other products.

The market for treatments of anemia in CKD in China is highly competitive.

Even if roxadustat is approved in China, it will face intense competition in the market for treatments of anemia in CKD. Roxadustat would compete with ESAs, which are offered by established multinational pharmaceutical companies such as Kyowa Hakko Kirin China Pharmaceutical Co., Ltd. and Roche and Chinese pharmaceutical companies such as 3SBio Inc. and Di'ao Group Chengdu Diao Jiuhong Pharmaceutical Factory. Many of these competitors have substantially greater name recognition, scientific, financial and marketing resources as well as established distribution capabilities than we do. Many of our competitors have more resources to develop or acquire, and more experience in developing or acquiring, new products and in creating market awareness for those products. Many of these competitors have significantly more experience than we have in navigating the Chinese regulatory framework regarding the development, manufacturing and marketing of drugs in China, as well as in marketing and selling anemia products in China. Additionally, we believe that most patients with anemia in CKD in China are currently being treated with traditional Chinese medicine, which is widely accepted and highly prevalent in China. Traditional Chinese medicine treatments are often oral and thus convenient and low-cost, and practitioners of traditional Chinese medicine are numerous and accessible in China. As a result, it may be difficult to persuade patients with anemia in CKD to switch from traditional Chinese medicine to roxadustat.

The Chinese government is implementing a new "Two Invoices" regulation which could impact the way we structure our distributorship relationships for roxadustat in China.

The Chinese government is expected to implement a regulation for implementation in the 31 Chinese provinces. Although we expect interpretation to vary the impact of this regulation across provinces, there may be a negative impact on our current distribution plans. For example, if the new policy is implemented in its entirety as proposed, and adhered to strictly by a local province, the restrictions on pricing and invoicing and how pharmaceutical product distribution compensation in China is implemented might negatively affect the structure of the FibroGen-AstraZeneca commercial distribution plan by imposing higher costs or slowing our ability under the agreement to sell products to our principal customers. Any change in distribution would be expected to have an adverse impact on the cost of delivery of product to the end user customer, potentially raising cost of operations through the chain of distribution and potentially delaying launch or initial sales. Although we have time to prepare to some degree in advance of our commercial launch, we may not have sufficient visibility and understanding of the implementation across some or all of the various provinces, the result of which may be a delay in the planned distribution efforts and near-term potential for sales growth in China for roxadustat as we and our distribution partners understand and adjust our distribution plans in response to the new regulation.

There is no assurance that roxadustat will be included in the Medical Insurance Catalogs.

Eligible participants in the national basic medical insurance program in China, which consists of mostly urban residents, are entitled to reimbursement from the social medical insurance fund for up to the entire cost of medicines that are included in the Medical Insurance Catalogs. Refer to "Business - Government Regulation - Regulation in China." We believe that the inclusion of a drug in the Medical Insurance Catalogs can substantially improve the sales of a drug. The Ministry of Labor and Social Security in China ("MLSS") together with other government authorities, select medicines to be included in the Medical Insurance Catalogs based on a variety of factors, including treatment requirements, frequency of use, effectiveness and price. The MLSS also occasionally removes medicines from such catalogs. There can be no assurance that roxadustat will be included, and once included, remain in the Medical Insurance Catalogs. The exclusion or removal of roxadustat from the Medical Insurance Catalogs may materially and adversely affect sales of roxadustat.

We may not be successful in the tender processes for the purchase of medicines by state-owned and state-controlled hospitals.

Most hospitals in China participate in collective tender processes for the purchase of medicines listed in the Medical Insurance Catalogs and medicines that are consumed in large volumes and commonly prescribed for clinical uses. During a collective tender process, the hospitals will establish a committee consisting of recognized pharmaceutical experts. The committee will assess the bids submitted by the various participating pharmaceutical manufacturers, taking into consideration, among other things, the quality and price of the drug product and the service and reputation of the manufacturer. Only drug products that have been selected in the collective tender processes may be purchased by participating hospitals. If we are unable to win purchase contracts through the collective tender processes in which we decide to participate, there will be limited demand for roxadustat, and sales revenues from roxadustat will be materially and adversely affected.

Even if FG-5200 can be manufactured successfully and achieve regulatory approval, we may not achieve commercial success.

We have not yet received a license to manufacture FG-5200 in our Beijing manufacturing facility or at scale, and we will have to show that FG-5200 from our China manufacturing facility meets the applicable regulatory requirements. There can be no assurance that we can meet these requirements or that FG-5200 can be approved for development, manufacture and sale in China.

Even if we are able to manufacture and develop FG-5200 as a medical device in China, the size and length of any potential clinical trials required for approval are uncertain and we are unable to predict the time and investment required to obtain regulatory approval. Moreover, even if FG-5200 can be successfully developed for approval in China, our product candidate would require extensive training and investment in assisting physicians in the use of FG-5200.

The retail prices of any product candidates that we develop may be subject to control, including periodic downward adjustment, by Chinese government authorities.

The price for pharmaceutical products is highly regulated in China, both at the national and provincial level. Price controls may reduce prices to levels significantly below those that would prevail in less regulated markets or limit the volume of products which may be sold, either of which may have a material and adverse effect on potential revenues from sales of roxadustat in China. Moreover, the process and timing for the implementation of price restrictions is unpredictable, which may cause potential revenues from the sales of roxadustat to fluctuate from period to period.

If our planned business activities in China fall within a restricted category under the China Catalog for Guidance for Foreign Investment, we will need to operate in China through a variable interest entity ("VIE") structure.

The China Catalog for Guidance for Foreign Investment sets forth the industries and sectors that the Chinese government encourages and restricts with respect to foreign investment and participation. The Catalog for Guidance for Foreign Investment is subject to revision from time to time by the China Ministry of Commerce. While we currently do not believe the development and marketing of roxadustat falls within a restricted category under the Catalog for Guidance for Foreign Investment, if roxadustat does fall under such a restricted category, we will need to operate in China through a VIE structure. A VIE structure involves a wholly foreign-owned enterprise that would control and receive the economic benefits of a domestic Chinese company through various contractual relationships. Such a structure would subject us to a number of risks that may have an adverse effect on our business, including that the Chinese government may determine that such contractual arrangements do not comply with applicable regulations, Chinese tax authorities may require us to pay additional taxes, shareholders of our VIEs may have potential conflicts of interest with us, and we may lose the ability to use and enjoy assets held by our VIEs that are important to the operations of our business if such entities go bankrupt or become subject to dissolution or liquidation proceedings. VIE structures in China have come under increasing scrutiny from accounting firms and the SEC staff. If we do attempt to use a VIE structure and are unsuccessful in structuring it so as to qualify as a VIE, we would not be able to consolidate the financial statements of the VIE with our financial statements, which could have a material adverse effect on our operating results and financial condition.

FibroGen Beijing would be subject to restrictions on paying dividends or making other payments to us, which may restrict our ability to satisfy our liquidity requirements.

We plan to conduct all of our business in China through FibroGen China Anemia Holdings, Ltd. and FibroGen Beijing. We may rely on dividends and royalties paid by FibroGen Beijing for a portion of our cash needs, including the funds necessary to service any debt we may incur and to pay our operating expenses. The payment of dividends by FibroGen Beijing is subject to limitations. Regulations in China currently permit payment of dividends only out of accumulated profits as determined in accordance with accounting standards and regulations in China. FibroGen Beijing is not permitted to distribute any profits until losses from prior fiscal years have been recouped and in any event must maintain certain minimum capital requirements. FibroGen Beijing is also required to set aside at least 10.0% of its after-tax profit based on Chinese accounting standards each year to its statutory reserve fund until the cumulative amount of such reserves reaches 50.0% of its registered capital. Statutory reserves are not distributable as cash dividends. In addition, if FibroGen Beijing incurs debt on its own behalf in the future, the agreements governing such debt may restrict its ability to pay dividends or make other distributions to us. As of December 31, 2017, approximately \$11.2 million of our cash and cash equivalents is held in China.

Any capital contributions from us to FibroGen Beijing must be approved by the Ministry of Commerce in China, and failure to obtain such approval may materially and adversely affect the liquidity position of FibroGen Beijing.

The Ministry of Commerce in China or its local counterpart must approve the amount and use of any capital contributions from us to FibroGen Beijing, and there can be no assurance that we will be able to complete the necessary government registrations and obtain the necessary government approvals on a timely basis, or at all. If we fail to do so, we may not be able to contribute additional capital to fund our Chinese operations, and the liquidity and financial position of FibroGen Beijing may be materially and adversely affected.

We may be subject to currency exchange rate fluctuations and currency exchange restrictions with respect to our operations in China, which could adversely affect our financial performance.

If roxadustat is approved for sale in China, most of our product sales will occur in local Chinese currency and our operating results will be subject to volatility from currency exchange rate fluctuations. To date, we have not hedged against the risks associated with fluctuations in exchange rates and, therefore, exchange rate fluctuations could have an adverse impact on our future operating results. Changes in value of the Renminbi against the U.S. dollar, Euro and other currencies is affected by, among other things, changes in China's political and economic conditions. Currently, the Renminbi is permitted to fluctuate within a narrow and managed band against a basket of certain foreign currencies. Any significant currency exchange rate fluctuations may have a material adverse effect on our business and financial condition.

In addition, the Chinese government imposes controls on the convertibility of the Renminbi into foreign currencies and the remittance of foreign currency out of China for certain transactions. Shortages in the availability of foreign currency may restrict the ability of FibroGen Beijing to remit sufficient foreign currency to pay dividends or other payments to us, or otherwise satisfy their foreign currency-denominated obligations. Under existing Chinese foreign exchange regulations, payments of current account items, including profit distributions, interest payments and balance of trade, can be made in foreign currencies without prior approval from the State Administration of Foreign Exchange ("SAFE") by complying with certain procedural requirements. However, approval from SAFE or its local branch is required where Renminbi is to be converted into foreign currency and remitted out of China to pay capital expenses such as the repayment of loans denominated in foreign currencies. The Chinese government may also at its discretion restrict access in the future to foreign currencies for current account transactions. If the foreign exchange control system prevents us from obtaining sufficient foreign currency to satisfy our operational requirements, our liquidity and financial position may be materially and adversely affected.

Because FibroGen Beijing's funds are held in banks that do not provide insurance, the failure of any bank in which FibroGen Beijing deposits its funds could adversely affect our business.

Banks and other financial institutions in China do not provide insurance for funds held on deposit. As a result, in the event of a bank failure, FibroGen Beijing may not have access to funds on deposit. Depending upon the amount of money FibroGen Beijing maintains in a bank that fails, its inability to have access to cash could materially impair its operations.

We may be subject to tax inefficiencies associated with our offshore corporate structure.

The tax regulations of the U.S. and other jurisdictions in which we operate are extremely complex and subject to change. New laws, new interpretations of existing laws, such as the Base Erosion Profit Shifting project initiated by the Organization for Economic Co-operation and Development and any legislation proposed by the relevant taxing authorities, or limitations on our ability to structure our operations and intercompany transactions may lead to inefficient tax treatment of our revenue, profits, royalties and distributions, if any are achieved.

In addition, we and our foreign subsidiaries have various intercompany transactions. We may not be able to obtain certain benefits under relevant tax treaties to avoid double taxation on certain transactions among our subsidiaries. If we are not able to avail ourselves of the tax treaties, we could be subject to additional taxes, which could adversely affect our financial condition and results of operations.

On December 22, 2017, the U.S. enacted the Tax Cuts and Jobs Act ("Tax Act") that instituted fundamental changes to the taxation of multinational corporations. The Tax Act includes changes to the taxation of foreign earnings by implementing a dividend exemption system, expansion of the current anti-deferral rules, a minimum tax on low-taxed foreign earnings and new measures to deter base erosion. The Tax Act also includes a permanent reduction in the corporate tax rate to 21%, repeal of the corporate alternative minimum tax, expensing of capital investment, and limitation of the deduction for interest expense. Furthermore, as part of the transition to the new tax system, a one-time transition tax is imposed on a U.S. shareholder's historical undistributed earnings of foreign affiliates. Although the Tax Act is generally effective January 1, 2018, GAAP requires recognition of the tax effects of new legislation during the reporting period that includes the enactment date, which was December 22, 2017.

As a result of the impacts of the Tax Act, the SEC provided guidance that allows us to record provisional amounts for those impacts, with the requirement that the accounting be completed in a period not to exceed one year from the date of enactment. As of December 31, 2017, we have not completed the accounting for the tax effects of the Tax Act. Therefore, we have recorded provisional amounts for the effects of the Tax Act. The primary impact of the Tax Act relates to the re-measurement of deferred tax assets and liabilities resulting from the change in the corporate tax rate ("Corporate Tax Rate Change"). We are evaluating other accounting policies with respect to other provisions of the Tax Act.

Our foreign operations, particularly those in China, are subject to significant risks involving the protection of intellectual property.

We seek to protect the products and technology that we consider important to our business by pursuing patent applications in China and other countries, relying on trade secrets or pharmaceutical regulatory protection or employing a combination of these methods. We note that the filing of a patent application does not mean that we will be granted a patent, or that any patent eventually granted will be as broad as requested in the patent application or will be sufficient to protect our technology. There are a number of factors that could cause our patents, if granted, to become invalid or unenforceable or that could cause our patent applications not to be granted, including known or unknown prior art, deficiencies in the patent application, or lack of originality of the technology. Furthermore, the terms of our patents are limited. The patents we hold and the patents that may be granted from our currently pending patent applications have, absent any patent term adjustment or extension, a twenty-year protection period starting from the date of application.

Intellectual property rights and confidentiality protections in China may not be as effective as those in the U.S. or other countries for many reasons, including lack of procedural rules for discovery and evidence, low damage awards, and lack of judicial independence. Implementation and enforcement of China intellectual property laws have historically been deficient and ineffective and may be hampered by corruption and local protectionism. Policing unauthorized use of proprietary technology is difficult and expensive, and we may need to resort to litigation to enforce or defend patents issued to us or to determine the enforceability and validity of our proprietary rights or those of others. The experience and capabilities of China courts in handling intellectual property litigation varies and outcomes are unpredictable. An adverse determination in any such litigation could materially impair our intellectual property rights and may harm our business.

We are subject to laws and regulations governing corruption, which will require us to develop and implement costly compliance programs.

We must comply with a wide range of laws and regulations to prevent corruption, bribery, and other unethical business practices, including the FCPA, anti-bribery and anti-corruption laws in other countries, particularly China. The creation and implementation of international business practices compliance programs is costly and such programs are difficult to enforce, particularly where reliance on third parties is required.

Anti-bribery laws prohibit us, our employees, and some of our agents or representatives from offering or providing any personal benefit to covered government officials to influence their performance of their duties or induce them to serve interests other than the missions of the public organizations in which they serve. Certain commercial bribery rules also prohibit offering or providing any personal benefit to employees and representatives of commercial companies to influence their performance of their duties or induce them to serve interests other than their employers. The FCPA also obligates companies whose securities are listed in the U.S. to comply with certain accounting provisions requiring us to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and devise and maintain an adequate system of internal accounting controls for international operations. The anti-bribery provisions of the FCPA are enforced primarily by the Department of Justice. The SEC is involved with enforcement of the books and records provisions of the FCPA.

Compliance with these anti-bribery laws is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, the anti-bribery laws present particular challenges in the pharmaceutical industry because in many countries including China, hospitals are state-owned or operated by the government, and doctors and other hospital employees are considered foreign government officials. Furthermore, in certain countries (China in particular), hospitals and clinics are permitted to sell pharmaceuticals to their patients and are primary or significant distributors of pharmaceuticals. Certain payments to hospitals in connection with clinical studies, procurement of pharmaceuticals and other work have been deemed to be improper payments to government officials that have led to vigorous anti-bribery law enforcement actions and heavy fines in multiple jurisdictions, particularly in the U.S. and China.

It is not always possible to identify and deter violations, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations.

In the pharmaceutical industry, corrupt practices include, among others, acceptance of kickbacks, bribes or other illegal gains or benefits by the hospitals and medical practitioners from pharmaceutical manufacturers, distributors or their third party agents in connection with the prescription of certain pharmaceuticals. If our employees, affiliates, distributors or third party marketing firms violate these laws or otherwise engage in illegal practices with respect to their sales or marketing of our products or other activities involving our products, we could be required to pay damages or heavy fines by multiple jurisdictions where we operate, which could materially and adversely affect our financial condition and results of operations. The Chinese government has also sponsored anti-corruption campaigns from time to time, which could have a chilling effect on any future marketing efforts by us to new hospital customers. There have been recent occurrences in which certain hospitals have denied access to sales representatives from pharmaceutical companies because the hospitals wanted to avoid the perception of corruption. If this attitude becomes widespread among our potential customers, our ability to promote our products to hospitals may be adversely affected.

As we expand our operations in China and other jurisdictions internationally, we will need to increase the scope of our compliance programs to address the risks relating to the potential for violations of the FCPA and other anti-bribery and anti-corruption laws. Our compliance programs will need to include policies addressing not only the FCPA, but also the provisions of a variety of anti-bribery and anti-corruption laws in multiple foreign jurisdictions, including China, provisions relating to books and records that apply to us as a public company, and include effective training for our personnel throughout our organization. The creation and implementation of anti-corruption compliance programs is costly and such programs are difficult to enforce, particularly where reliance on third parties is required. Violation of the FCPA and other anti-corruption laws can result in significant administrative and criminal penalties for us and our employees, including substantial fines, suspension or debarment from government contracting, prison sentences, or even the death penalty in extremely serious cases in certain countries. The SEC also may suspend or bar us from trading securities on U.S. exchanges for violation of the FCPA's accounting provisions. Even if we are not ultimately punished by government authorities, the costs of investigation and review, distraction of our personnel, legal defense costs, and harm to our reputation could be substantial and could limit our profitability or our ability to develop or commercialize our product candidates. In addition, if any of our competitors are not subject to the FCPA, they may engage in practices that will lead to their receipt of preferential treatment from foreign hospitals and enable them to secure business from foreign hospitals in ways that are unavailable to us.

Uncertainties with respect to the China legal system could have a material adverse effect on us.

The legal system of China is a civil law system primarily based on written statutes. Unlike in a common law system, prior court decisions may be cited for reference but are not binding. Because the China legal system continues to rapidly evolve, the interpretations of many laws, regulations and rules are not always uniform and enforcement of these laws, regulations and rules involve uncertainties, which may limit legal protections available to us. Moreover, decision makers in the China judicial system have significant discretion in interpreting and implementing statutory and contractual terms, which may render it difficult for FibroGen Beijing to enforce the contracts it has entered into with our business partners, customers and suppliers. Different government departments may have different interpretations of certain laws and regulations, and licenses and permits issued or granted by one government authority may be revoked by a higher government authority at a later time. Navigating the uncertainty and change in the China legal system will require the devotion of significant resources and time, and there can be no assurance that our contractual and other rights will ultimately be enforced.

Changes in China's economic, political or social conditions or government policies could have a material adverse effect on our business and operations.

The Chinese economy and Chinese society continue to undergo significant change. Adverse changes in the political and economic policies of the Chinese government could have a material adverse effect on the overall economic growth of China, which could adversely affect our ability to conduct business in China. The Chinese government continues to adjust economic policies to promote economic growth. Some of these measures benefit the overall Chinese economy, but may also have a negative effect on us. For example, our financial condition and results of operations in China may be adversely affected by government control over capital investments or changes in tax regulations. As the Chinese pharmaceutical industry grows and evolves, the Chinese government may also implement measures to change the structure of foreign investment in this industry. We are unable to predict the frequency and scope of such policy changes, any of which could materially and adversely affect FibroGen Beijing's liquidity, access to capital and its ability to conduct business in China. Any failure on our part to comply with changing government regulations and policies could result in the loss of our ability to develop and commercialize our product candidates in China.

Our operations in China subject us to various Chinese labor and social insurance laws, and our failure to comply with such laws may materially and adversely affect our business, financial condition and results of operations.

We are subject to China Labor Contract Law, which provides strong protections for employees and imposes many obligations on employers. The Labor Contract Law places certain restrictions on the circumstances under which employers may terminate labor contracts and require economic compensation to employees upon termination of employment, among other things. In addition, companies operating in China are generally required to contribute to labor union funds and the mandatory social insurance and housing funds. Any failure by us to comply with Chinese labor and social insurance laws may subject us to late fees, fines and penalties, or cause the suspension or termination of our ability to conduct business in China, any of which could have a material and adverse effect on business, results of operations and prospects.

Recent developments relating to the United Kingdom's referendum vote in favor of leaving the EU could adversely affect us.

The United Kingdom held a referendum on June 23, 2016 in which a majority voted for the United Kingdom's withdrawal from the EU, commonly referred to as "Brexit". As a result of this vote, negotiations are expected to commence to determine the terms of the United Kingdom's withdrawal from the EU as well as its relationship with the EU going forward, including the terms of trade between the United Kingdom and the EU. The effects of the United Kingdom's withdrawal from the EU, and the perceptions as to its impact, are expected to be far-reaching and may adversely affect business activity and economic conditions in Europe and globally and could continue to contribute to instability in global financial markets, including foreign exchange markets. The United Kingdom's withdrawal from the EU could also have the effect of disrupting the free movement of goods, services and people between the United Kingdom and the EU and could also lead to legal uncertainty and potentially divergent national laws and regulations as the United Kingdom determines which EU laws to replace or replicate, including laws that could impact our ability, or our collaborator's ability in the case of roxadustat, to obtain approval of our products or sell our products in the United Kingdom. However, the full effects of such withdrawal are uncertain and will depend on any agreements the United Kingdom may make to retain access to EU markets. Lastly, as a result of the United Kingdom's withdrawal from the EU, other European countries may seek to conduct referenda with respect to their continuing membership with the EU. Given these possibilities and others we may not anticipate, as well as the lack of comparable precedent, the full extent to which our business, results of operations and financial condition could be adversely affected by the United Kingdom's withdrawal from the EU is uncertain.

Risks Related to the Operation of Our Business

We may encounter difficulties in managing our growth and expanding our operations successfully.

As we seek to advance our product candidates through clinical trials and commercialization, we will need to expand our development, regulatory, manufacturing, commercialization and administration capabilities or contract with third parties to provide these capabilities for us. As our operations expand and we continue to undertake the efforts and expense to operate as a public reporting company, we expect that we will need to increase the responsibilities on members of management in order to manage any future growth effectively. Our failure to accomplish any of these steps could prevent us from successfully implementing our strategy and maintaining the confidence of investors in our company.

If we fail to attract and keep senior management and key personnel, in particular our chief executive officer, we may be unable to successfully develop our product candidates, conduct our clinical trials and commercialize our product candidates.

We are highly dependent on our chief executive officer, Thomas B. Neff, and other members of our senior management team. The loss of the services of Mr. Neff or any of these other individuals would be expected to significantly negatively impact the development and commercialization of our product candidates, our existing collaborative relationships and our ability to successfully implement our business strategy.

Recruiting and retaining qualified commercial, development, scientific, clinical and manufacturing personnel are and will continue to be critical to our success. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory approval of and commercialize product candidates. We may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the intense competition among numerous biopharmaceutical companies for similar personnel.

There is also significant competition, in particular in the San Francisco Bay Area, for the hiring of experienced and qualified personnel, which increases the importance of retention of our existing personnel. If we are unable to continue to attract and retain personnel with the quality and experience applicable to our product candidates, our ability to pursue our strategy will be limited and our business and operations would be adversely affected.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our product candidates.

We face an inherent risk of product liability as a result of the clinical testing, manufacturing and commercialization of our product candidates. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in a product, negligence, strict liability or breach of warranty. Claims could also be asserted under state consumer protection acts. If we are unable to obtain insurance coverage at levels that are appropriate to maintain our business and operations, or if we are unable to successfully defend ourselves against product liability claims, we may incur substantial liabilities or otherwise cease operations. Product liability claims may result in:

- termination of further development of unapproved product candidates or significantly reduced demand for any approved products;
- material costs and expenses to defend the related litigation;
- a diversion of time and resources across the entire organization, including our executive management;
- product recalls, withdrawals or labeling restrictions;
- · termination of our collaboration relationships or disputes with our collaboration partners; and
- reputational damage negatively impacting our other product candidates in development.

If we fail to obtain and retain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims, we may not be able to continue to develop our product candidates. We maintain product liability insurance in a customary amount for the stage of development of our product candidates. Although we believe that we have sufficient coverage based on the advice of our third party advisors, there can be no assurance that such levels will be sufficient for our needs. Moreover, our insurance policies have various exclusions, and we may be in a dispute with our carrier as to the extent and nature of our coverage, including whether we are covered under the applicable product liability policy. If we are not able to ensure coverage or are required to pay substantial amounts to settle or otherwise contest the claims for product liability, our business and operations would be negatively affected.

Our business and operations would suffer in the event of computer system failures.

Despite the implementation of security measures, our internal computer systems, and those of our CROs, collaboration partners, and other third parties on which we rely, are vulnerable to damage from computer viruses, unauthorized access, natural disasters, fire, terrorism, war and telecommunication and electrical failures. We upgraded our disaster and data recovery capabilities in June 2017, however, to the extent that any disruption or security breach, in particular with our partners' operations, results in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and it could result in a material disruption and delay of our drug development programs. For example, the loss of clinical trial data from completed, ongoing or planned clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data.

We depend on sophisticated information technology systems to operate our business and a cyber-attack or other breach of these systems could have a material adverse effect on our business.

We rely on information technology systems to process, transmit and store electronic information in our day-to-day operations. The size and complexity of our information technology systems makes them vulnerable to a cyber-attack, malicious intrusion, breakdown, destruction, loss of data privacy or other significant disruption. While we have recently upgraded our disaster data recovery program, a successful attack could result in the theft or destruction of intellectual property, data, or other misappropriation of assets, or otherwise compromise our confidential or proprietary information and disrupt our operations. Cyber-attacks are becoming more sophisticated and frequent. We have invested in our systems and the protection and recoverability of our data to reduce the risk of an intrusion or interruption, and we monitor and test our systems on an ongoing basis for any current or potential threats. There can be no assurance that these measures and efforts will prevent future interruptions or breakdowns. If we fail to maintain or protect our information technology systems and data integrity effectively or fail to anticipate, plan for or manage significant disruptions to these systems, we could have difficulty preventing, detecting and controlling such cyber-attacks and any such attacks could result in losses described above as well as disputes with physicians, patients and our partners, regulatory sanctions or penalties, increases in operating expenses, expenses or lost revenues or other adverse consequences, any of which could have a material adverse effect on our business, results of operations, financial condition, prospects and cash flows.

Our headquarters and data storage facilities are located near known earthquake fault zones. The occurrence of an earthquake, fire or any other catastrophic event could disrupt our operations or the operations of third parties who provide vital support functions to us, which could have a material adverse effect on our business, results of operations and financial condition.

We and some of the third party service providers on which we depend for various support functions, such as data storage, are vulnerable to damage from catastrophic events, such as power loss, natural disasters, terrorism and similar unforeseen events beyond our control. Our corporate headquarters and other facilities are located in the San Francisco Bay Area, which in the past has experienced severe earthquakes and fires.

We do not carry earthquake insurance. Earthquakes or other natural disasters could severely disrupt our operations, and have a material adverse effect on our business, results of operations, financial condition and prospects.

If a natural disaster, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters, damaged critical infrastructure, or otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place are unlikely to provide adequate protection in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which, particularly when taken together with our lack of earthquake insurance, could have a material adverse effect on our business.

Furthermore, integral parties in our supply chain are operating from single sites, increasing their vulnerability to natural disasters or other sudden, unforeseen and severe adverse events. If such an event were to affect our supply chain, it could have a material adverse effect on our business.

Risks Related to Our Common Stock

The market price of our common stock may be highly volatile, and you may not be able to resell your shares at or above your purchase price.

In general, pharmaceutical, biotechnology and other life sciences company stocks have been highly volatile in the current market. The volatility of pharmaceutical, biotechnology and other life sciences company stocks is sometimes unrelated to the operating performance of particular companies and biotechnology and life science companies stocks often respond to trends and perceptions rather than financial performance. In particular, the market price of shares of our common stock could be subject to wide fluctuations in response to the following factors:

- results of clinical trials of our product candidates, including roxadustat and pamrevlumab;
- the timing of the release of results of and regulatory updates regarding our clinical trials;
- the level of expenses related to any of our product candidates or clinical development programs;
- results of clinical trials of our competitors' products;
- safety issues with respect to our product candidates or our competitors' products;
- regulatory actions with respect to our product candidates and any approved products or our competitors' products;
- fluctuations in our financial condition and operating results, which will be significantly affected by the manner in which we recognize
 revenue from the achievement of milestones under our collaboration agreements;
- adverse developments concerning our collaborations and our manufacturers;
- the termination of a collaboration or the inability to establish additional collaborations;
- the publication of research reports by securities analysts about us or our competitors or our industry or negative recommendations or withdrawal of research coverage by securities analysts;
- the inability to obtain adequate product supply for any approved drug product or inability to do so at acceptable prices;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- the ineffectiveness of our internal controls;
- our failure or the failure of our competitors to meet analysts' projections or guidance that we or our competitors may give to the
 market:
- · additions and departures of key personnel;
- announced strategic decisions by us or our competitors;
- changes in legislation or other regulatory developments affecting our product candidates or our industry;
- fluctuations in the valuation of the biotechnology industry and particular companies perceived by investors to be comparable to us;
- sales of our common stock by us, our insiders or our other stockholders;
- speculation in the press or investment community;
- announcement or expectation of additional financing efforts;
- · announcements of investigations or regulatory scrutiny of our operations or lawsuits filed against us;
- changes in accounting principles;
- · activities of the government of China, including those related to the pharmaceutical industry as well as industrial policy generally;
- performance of other U.S. publicly traded companies with significant operations in China;
- terrorist acts, acts of war or periods of widespread civil unrest;
- natural disasters such as earthquakes and other calamities;
- changes in market conditions for biopharmaceutical stocks;

- · changes in general market and economic conditions; and
- the other factors described in this "Risk Factors" section.

As a result of fluctuations caused by these and other factors, comparisons of our operating results across different periods may not be accurate indicators of our future performance. Any fluctuations that we report in the future may differ from the expectations of market analysts and investors, which could cause the price of our common stock to fluctuate significantly. Moreover, securities class action litigation has often been initiated against companies following periods of volatility in their stock price. This type of litigation could result in substantial costs and divert our management's attention and resources, and could also require us to make substantial payments to satisfy judgments or to settle litigation.

We have broad discretion in the use of the net proceeds from our underwritten public offerings of common stock completed on April 11, 2017 (the "April 2017 Offering") and completed on August 24, 2017 (the "August 2017 Offering") and may not use them effectively.

The net proceeds from the April 2017 Offering is intended to be used to fund the expansion of product development in China, including developing roxadustat in additional indications beyond CKD, manufacturing and commercialization activities, as well as for general corporate purposes. The net proceeds from the August 2017 Offering is intended to be used to fund the expansion of product development, including our development of pamrevlumab beyond current Phase 2 programs, manufacturing and commercialization activities, as well as for general corporate purposes. These general corporate purposes, may include, among other things, funding research and development, clinical trials, vendor payables, potential regulatory submissions, hiring additional personnel and capital expenditures. However, we have no current commitments or obligations to use the net proceeds in the manner described above. Our management has broad discretion in the application of the balance of the net proceeds from the April 2017 Offering and the August 2017 Offering, and could spend the proceeds in ways our stockholders may not agree with or that fails to improve our business or enhance the value of our common stock. The failure by our management to use these funds effectively could result in financial losses that could harm our business, cause the price of our common stock to decline and delay the development of our product candidates.

If securities or industry analysts do not continue to publish research or reports about our business, or if they change their recommendations regarding our stock adversely, our stock price and trading volume could decline.

The trading market for our common stock will be influenced by the research and reports that industry or securities analysts publish about us or our business. If one or more of the analysts who cover us downgrade our stock, our stock price would likely decline. If one or more of these analysts cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which in turn could cause our stock price or trading volume to decline.

Our principal stockholders and management own a significant percentage of our stock and will be able to exercise significant influence over matters subject to stockholder approval.

As of January 31, 2018, our executive officers, directors and principal stockholders, together with their respective affiliates, owned approximately 27.26% of our common stock, including shares subject to outstanding options that are exercisable within 60 days after such date and shares issuable upon settlement of restricted stock units that will vest within 60 days after such date. This percentage is based upon information supplied by officers, directors and principal stockholders and Schedules 13D and 13G, if any, filed with the SEC, which information may not be accurate as of January 31, 2018. Accordingly, these stockholders will be able to exert a significant degree of influence over our management and affairs and over matters requiring stockholder approval, including the election of our board of directors and approval of significant corporate transactions. The interests of this group may differ from those of other stockholders and they may vote their shares in a way that is contrary to the way other stockholders vote their shares. This concentration of ownership could have the effect of entrenching our management and/or the board of directors, delaying or preventing a change in our control or otherwise discouraging a potential acquirer from attempting to obtain control of us, which in turn could have a material and adverse effect on the fair market value of our common stock.

Additional remedial measures that may be imposed in the proceedings instituted by the SEC against five China based accounting firms, including the Chinese affiliate of our independent registered public accounting firm, could result in our consolidated financial statements being determined to not be in compliance with the requirements of the Exchange Act.

In late 2012, the SEC commenced administrative proceedings under Rule 102(e) of its Rules of Practice and also under the Sarbanes-Oxley Act of 2002 against the Chinese affiliates of the "big four" accounting firms, including PricewaterhouseCoopers Zhong Tian CPAs Limited, the Chinese affiliate of our independent registered public accounting firm. The Rule 102(e) proceedings initiated by the SEC relate to these firms' failure to produce documents, including audit work papers, in response to the request of the SEC pursuant to Section 106 of the Sarbanes-Oxley Act of 2002, as the auditors located in China are not in a position lawfully to produce documents directly to the SEC because of restrictions under Chinese law and specific directives issued by the China Securities Regulatory Commission ("CSRC"). The issues raised by the proceedings are not specific to our auditors or to us.

In January 2014, an administrative law judge reached an initial decision that the Chinese affiliates of the "big four" accounting firms should be barred from practicing before the SEC for a period of six months. In February 2015, the Chinese affiliates of the "big four" accounting firms each agreed to a censure and to pay a fine to the SEC to settle the dispute and avoid suspension of their ability to practice before the SEC and audit U.S.-listed companies. The settlement required the firms to follow detailed procedures and to seek to provide the SEC with access to Chinese firms' audit documents via the CSRC. If future document productions fail to meet specified criteria, the SEC retains authority to impose a variety of additional remedial measures on the firms depending on the nature of the failure.

We cannot predict if the SEC will further review the four firms' compliance with specified criteria or if such further review would result in the SEC imposing additional penalties such as suspensions or commencing any further administrative proceedings. Although it does not play a substantial role (as defined under PCAOB standards) in the audit of our consolidated financial statements, if PricewaterhouseCoopers Zhong Tian CPAs Limited were denied, temporarily, the ability to practice before the SEC, our ability to produce audited consolidated financial statements for our company could be affected and we could be determined not to be in compliance with the requirements of the Exchange Act. Such a determination could ultimately lead to the delisting of our shares from the NASDAQ Global Select Market or deregistration from the SEC, or both, which would substantially reduce or effectively terminate the trading of our stock.

We may engage in future acquisitions that could disrupt our business, cause dilution to our stockholders and harm our business, results of operations, financial condition and cash flows and future prospects.

While we currently have no specific plans to acquire any other businesses, we may, in the future, make acquisitions of, or investments in, companies that we believe have products or capabilities that are a strategic or commercial fit with our present or future product candidates and business or otherwise offer opportunities for our company. In connection with these acquisitions or investments, we may:

- issue stock that would dilute our existing stockholders' percentage of ownership;
- · incur debt and assume liabilities; and
- incur amortization expenses related to intangible assets or incur large and immediate write-offs.

We may not be able to complete acquisitions on favorable terms, if at all. If we do complete an acquisition, we cannot assure you that it will ultimately strengthen our competitive position or that it will be viewed positively by customers, financial markets or investors. Furthermore, future acquisitions could pose numerous additional risks to our operations, including:

- · problems integrating the purchased business, products or technologies, or employees or other assets of the acquisition target;
- increases to our expenses;
- disclosed or undisclosed liabilities of the acquired asset or company;
- diversion of management's attention from their day-to-day responsibilities;
- reprioritization of our development programs and even cessation of development and commercialization of our current product candidates:
- harm to our operating results or financial condition;
- entrance into markets in which we have limited or no prior experience; and
- potential loss of key employees, particularly those of the acquired entity.

We may not be able to complete any acquisitions or effectively integrate the operations, products or personnel gained through any such acquisition.

Provisions in our charter documents and Delaware law may have anti-takeover effects that could discourage an acquisition of us by others, even if an acquisition would be beneficial to our stockholders, and may prevent attempts by our stockholders to replace or remove our current directors or management.

Provisions in our amended and restated certificate of incorporation and amended and restated bylaws contain provisions that may have the effect of discouraging, delaying or preventing a change in control of us or changes in our management. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

- authorize "blank check" preferred stock, which could be issued by our board of directors without stockholder approval and may contain voting, liquidation, dividend and other rights superior to our common stock;
- create a classified board of directors whose members serve staggered three-year terms;
- specify that special meetings of our stockholders can be called only by our board of directors pursuant to a resolution adopted by a
 majority of the total number of directors;
- prohibit stockholder action by written consent;
- establish an advance notice procedure for stockholder approvals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our board of directors;
- provide that our directors may be removed prior to the end of their term only for cause;
- provide that vacancies on our board of directors may be filled only by a majority of directors then in office, even though less than a
 quorum;
- require a supermajority vote of the holders of our common stock or the majority vote of our board of directors to amend our bylaws;
- require a supermajority vote of the holders of our common stock to amend the classification of our board of directors into three classes and to amend certain other provisions of our certificate of incorporation.

These provisions, alone or together, could delay or prevent hostile takeovers and changes in control or changes in our management by making it more difficult for stockholders to replace members of our board of directors, which is responsible for appointing the members of our management.

Moreover, because we are incorporated in Delaware, we are governed by certain anti-takeover provisions under Delaware law which may discourage, delay or prevent someone from acquiring us or merging with us whether or not it is desired by or beneficial to our stockholders. We are subject to the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

Any provision of our amended and restated certificate of incorporation, our amended and restated bylaws or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our common stock, and could also affect the price that some investors are willing to pay for our common stock.

Changes in our tax provision or exposure to additional tax liabilities could adversely affect our earnings and financial condition.

As a multinational corporation, we are subject to income taxes in the U.S. and various foreign jurisdictions. Significant judgment is required in determining our global provision for income taxes and other tax liabilities. In the ordinary course of a global business, there are intercompany transactions and calculations where the ultimate tax determination is uncertain. Our income tax returns are subject to audits by tax authorities. Although we regularly assess the likelihood of adverse outcomes resulting from these examinations to determine our tax estimates, a final determination of tax audits or tax disputes could have an adverse effect on our results of operations and financial condition.

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We are also subject to non-income taxes, such as payroll, sales, use, value-added, net worth, property, gross receipts, and goods and services taxes in the U.S., state and local, or various foreign jurisdictions. We are subject to audit and assessments by tax authorities with respect to these non-income taxes and may have exposure to additional non-income tax liabilities which could have an adverse effect on our results of operations and financial condition.

On December 22, 2017, the U.S. enacted the Tax Act that instituted fundamental changes to the taxation of multinational corporations. The Tax Act includes changes to the taxation of foreign earnings by implementing a dividend exemption system, expansion of the current anti-deferral rules, a minimum tax on low-taxed foreign earnings and new measures to deter base erosion. The Tax Act also includes a permanent reduction in the corporate tax rate to 21%, repeal of the corporate alternative minimum tax, expensing of capital investment, and limitation of the deduction for interest expense. Furthermore, as part of the transition to the new tax system, a one-time transition tax is imposed on a U.S. shareholder's historical undistributed earnings of foreign affiliates. Although the Tax Act is generally effective January 1, 2018, GAAP requires recognition of the tax effects of new legislation during the reporting period that includes the enactment date, which was December 22, 2017.

As a result of the impacts of the Tax Act, the SEC provided guidance that allows us to record provisional amounts for those impacts, with the requirement that the accounting be completed in a period not to exceed one year from the date of enactment. As of December 31, 2017, we have not completed the accounting for the tax effects of the Tax Act. Therefore, we have recorded provisional amounts for the effects of the Tax Act. The primary impact of the Tax Act relates to the re-measurement of deferred tax assets and liabilities resulting from the Corporate Tax Rate Change. We are evaluating other accounting policies with respect to other provisions of the Tax Act.

Our amended and restated certificate of incorporation designates the state or federal courts located in the State of Delaware as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our amended and restated certificate of incorporation provides that, subject to limited exceptions, the state and federal courts located in the State of Delaware will be the sole and exclusive forum for (1) any derivative action or proceeding brought on our behalf, (2) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers or other employees to us or our stockholders, (3) any action asserting a claim against us arising pursuant to any provision of the Delaware General Corporation Law, our amended and restated certificate of incorporation or our amended and restated by-laws, or (4) any other action asserting a claim against us that is governed by the internal affairs doctrine. Any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock shall be deemed to have notice of and to have consented to the provisions of our amended and restated certificate of incorporation described above. This choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and our directors, officers and employees. Alternatively, if a court were to find these provisions of our amended and restated certificate of incorporation inapplicable to, or unenforceable in respect of, one or more of the specified types of actions or proceedings, we may incur additional costs associated with resolving such matters in other jurisdictions, which could adversely affect our business and financial condition.

Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be your sole source of gain and you may never receive a return on your investment.

You should not rely on an investment in our common stock to provide dividend income. We do not anticipate that we will pay any cash dividends to holders of our common stock in the foreseeable future and investors seeking cash dividends should not purchase our common stock. We plan to retain any earnings to invest in our product candidates and maintain and expand our operations. Therefore, capital appreciation, or an increase in your stock price, which may never occur, may be the only way to realize any return on your investment.

ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

ITEM 2. PROPERTIES

Our corporate and research and development operations are located in San Francisco, California, where we lease approximately 234,000 square feet of office and laboratory space with approximately 35,000 square feet subleased. The lease for our San Francisco headquarters expires in 2023. We also lease approximately 67,000 square feet of office and manufacturing space in Beijing, China. Our lease in China expires in 2021. We are constructing a commercial manufacturing facility of approximately 5,500 square meters in Cangzhou, China, on approximately 33,000 square meters of land. Our right to use such land expires in 2068. We believe our facilities are adequate for our current needs and that suitable additional or substitute space would be available if needed.

Exhibit 31.1

CERTIFICATION

- I, Thomas B. Neff., certify that;
- 1. I have reviewed this annual report on Form 10-K of FibroGen, Inc.;
- 2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
- 3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
- 4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in the Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:
- (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
- (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
- (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
- (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
- 5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
- (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
- (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 27, 2018 /s/ Thomas B. Neff

Thomas B. Neff Chief Executive Officer and Chairman of the Board (Principal Executive Officer)

Exhibit 31.2

CERTIFICATION

- I, Pat Cotroneo, certify that;
- 1. I have reviewed this annual report on Form 10-K of FibroGen, Inc.;
- 2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
- 3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
- 4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in the Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:
- (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
- (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
- (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
- (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
- 5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
- (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
- (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 27, 2018 /s/ Pat Cotroneo

Pat Cotroneo

Vice President, Finance and Chief Financial Officer (Principal Financial Officer)

Exhibit 32.1

CERTIFICATION

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), Thomas B. Neff, Chief Executive Officer of FibroGen, Inc. (the "Company"), and Pat Cotroneo, Chief Financial Officer of the Company, each hereby certifies that, to the best of his knowledge:

- 1. The Company's Annual Report on Form 10-K for the year ended December 31, 2017 (the "Annual Report"), to which this Certification is attached as Exhibit 32.1, fully complies with the requirements of Section 13(a) or Section 15(d) of the Exchange Act, and
- 2. The information contained in the Annual Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

In Witness Whereof, the undersigned have set their hands hereto as of the 27th day of February, 2018.

/s/ Thomas B. Neff	/s/ Pat Cotroneo	
Thomas B. Neff	Pat Cotroneo	
Chief Executive Officer	Chief Financial Officer	

This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of FibroGen, Inc. under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.

EXHIBIT B

A Phase 3, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of Roxadustat for the Treatment of Anemia in Chronic Kidney Disease Patients not on Dialysis

ISN/Protocol 1517-CL-0608

ClinicalTrials.gov Identifier: NCT01887600

Date of Statistical Analysis Plan: Final Version 5.0, dated 02 Aug 2018

Sponsor: Astellas Pharma Europe B.V. (APEB)

Sylviusweg 62 2333 BE Leiden The Netherlands

SAP Final Version 5.0

ISN/Protocol 1517-CL-0608

STATISTICAL ANALYSIS PLAN

Final Version 5.0, dated 02 August 2018

A Phase 3, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of Roxadustat for the Treatment of Anemia in Chronic Kidney Disease Patients not on Dialysis

ISN: 1517-CL-0608

EudraCT number: 2012-005180-27

Sponsor name Astellas Pharma Europe B.V. (APEB) Sylviusweg 62, 2333 BE Leiden The Netherlands

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This confidential document is the property of the sponsor. No unpublished information contained in this document may be disclosed without prior written approval of the sponsor.

ISN/Protocol 1517-CL-0608

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I. LIST of ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (GPT)
ANCOVA	Analysis of Covariance
AnS	Anemia Subscale
anti-HCV Ab	Anti-hepatitis C Virus Antibody
APEB	Astellas Pharma Europe B.V.
Apo	Apolipoproteins
ASC	Analysis Set Classifications
ASP1517	FG-4592 (codename of investigational product) or roxadustat (international nonproprietary name)
AST	Aspartate Aminotransferase (GOT)
AT	Aminotransferase
ATC	Anatomical Therapeutic Chemical
BL	Baseline
BL Hb	Baseline Hemoglobin (please refer to key definitions for infoFrmation)
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CHr	Reticulocyte Hemoglobin Content
CI	Confidence Interval
CKD	Chronic Kidney Disease
СМН	Cochran-Mantel-Haenszel
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C Reactive Protein
CS	Classification Specifications
CSE	Composite Safety Endpoint
CSR	Clinical Study Report
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
dL	Deciliter
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram

Abbreviations	Description of abbreviations
eCRF	Electronic CRF
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
ЕН	Excessive Hematopoiesis
EOS	End of Study
EOT	End of Treatment
EQ-5D 5L	Health Related Quality of Life Questionnaire Consisting of Five Levels
ESA	Erythropoiesis Stimulating Agent
ESRD	End Stage Renal Disease
EU	European Union
EudraCT	Clinical trial database regulated by European Community
EWB	Emotional Well being
FACT-An	Functional Assessment of Cancer Therapy-Anemia
FACT-G	Functional Assessment of Cancer Therapy-General
FDA	Food and Drug Administration
FAS	Full Analysis Set
FG-4592	= ASP1517 (codename of investigational product) or roxadustat (international nonproprietary name)
FSI	First Subject In
FWB	Functional Well-being
g	gram
GDS	Global Data Science
GGT	Gamma Glutamyl Transferase
GM	Geometric Mean
Hb	Hemoglobin
HbA1c	Hemoglobin A1c; Glycated hemoglobin
HBsAG	Hepatitis B Surface Antigen
Hct	Hematocrit
HD	Hemodialysis
HDF	Hemodiafiltration
HDL	High-density Lipoprotein
HEENT	Head, Eyes, Ears, Neck and Throat
HIF	Hypoxia-inducible Factor
HIV	Human Immunodeficiency Virus
HR	Heart Rate
HRQoL	Health-Related Quality of Life
hs-CRP	High Sensitivity C-reactive protein

Abbreviations	Description of abbreviations
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH E3	Guidance for Industry Structure and Content of Clinical Study Reports
ICH E9	Statistical Principles for Clinical Trials
ICH E14	Guidance for Industry – Clinical Evaluation of QT/QTc
IEC	Independent Ethics Committee
IERC	Independent Event Review Committee
INN	International Nonproprietary Name
INR	International Normalized Ratio
IPCW	Inverse Probability of Censoring Weighting
IRT	Interactive Response Technology
ISN	International Study Number
IV	Intravenous(ly)
Kg	Kilograms
LDL	Low-density Lipoprotein
LA-CRF	Liver Abnormality Case Report Form
LFT	Liver Function Tests
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
LSO	Last Subject Out
MACE	Major cardiovascular adverse events: myocardial infarction, stroke, death from all causes
MACE+	Myocardial infarction, stroke, death from all causes, chronic heart failure requiring hospitalization, unstable angina requiring hospitalization
MAP	Mean Arterial Pressure
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	Myocardial Infarction
mL	Milliliters
Mg	Microgram
MMRM	Mixed Model of Repeated Measures
MSAP	Meta-Analysis Statistical Analysis Plan
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
О	Optional
PCS	Physical Component Score
PD	Protocol Deviation
PDAS	Pharmacodynamic Analysis Set

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Abbreviations	Description of abbreviations
PEY	Patient-exposure year
PF	Physical Functioning
PGIC	Patients' Global Impression of Change
PK	Pharmacokinetic
PKAS	Pharmacokinetic Analysis Set
PPS	Per Protocol Set
PT	Preferred Term
PWB	Physical Well-being
QoL	Quality of Life
QRS	QRS interval
QTc	QT Interval corrected for heart rate
QTcB	QTc calculated according to Bazett's formula
QTcF	QTc calculated according to Fridericia's formula
RBC	Red Blood Cell
RR	Respiratory Rate
RR Interval	Interval between successive Rs of the ECG
r-HuEPO	Recombinant Human Erythropoietin
RRT	Renal Replacement Therapy
SAE	Serious AE
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
SD	Standard Deviation
SI	International System of Units
SF-36	Short Form 36
SF-36 PCS	SF-36 Physical Component Score
SF-36 PF	SF-36 Physical Functioning
SF-36 MCS	SF-36 Mental Component Score
SF-36 VT	SF-36 Vitality
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SOP	Standard Operating Procedure
SPA	Special Protocol Assessment
SQ	Subcutaneous
sTfR	Soluble Transferrin Receptor
SWB	Social Well-being

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Abbreviations	Description of abbreviations
TEAE	Treatment-Emergent Adverse Event
TIBC	Total Iron-Binding Capacity
TIW	Thrice Weekly
TLF	Tables, Listings and Figures
TSAT	Transferrin Saturation (also known as FeSAT, iron saturation)
ULN	Upper Limit of Normal
USRDS	United States Renal Data System
VAS	Visual Analogue Scale
VT	Vitality
WBC	White Blood Cell
WHO-DRL	World Health Organization Drug Reference List
Wk(s)	Week(s)
WPAI:ANS	Work Productivity and Activity Impairment questionnaire: Anemic Symptoms

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List of Key Terms

Terms	Definition of terms
Adverse Event	An adverse event (AE) is as any untoward medical occurrence in a subject administered the study drug, roxadustat or placebo, or who has undergone study procedures and which does not necessarily have a causal relationship with this treatment. AE collection starts after obtaining signed informed consent and continues until the End of Study visit. AEs will not be collected during the period between first screen where subject has failed screening and first rescreening visit.
Baseline	1) Observed values/findings which are regarded as calibrated zero status in the present study; 2) Time when 'Baseline' is observed.
Baseline Hemoglobin (Hb) value	Baseline Hb is defined as the mean of four central laboratory Hb values: four latest Hb values prior or on the same date as first study drug intake (pre-dose).
Discontinuation	The act of concluding participation in either the study treatment or the study, prior to completion of all protocol-required elements, in a trial by an enrolled subject. Four categories of discontinuation are distinguished: a) dropout: Active discontinuation by a subject (also a noun referring to such a discontinued subject); b) investigator-initiated discontinuation (e.g., for cause); c) loss to follow-up: cessation of participation without notice or action by the subject; d) sponsor-initiated discontinuation. Note that subject discontinuation does not necessarily imply exclusion of subject data from analysis. "Termination" has a history of synonymous use, but is now considered non-standard.
Endpoint	Event or outcome that can be measured objectively to determine whether the intervention being studied is beneficial. Primary and secondary variables supporting objectives of the study are called endpoints.
Enroll	To register or enter into a clinical trial; transitive and intransitive. Informed consent precedes enrollment, which precedes or is contemporaneous with randomization.
Extended treatment period	Period of time that patient is treated from end of primary treatment period (52 weeks) up to 104 weeks
Hb Response	• Hb≥11.0 g/dL and a Hb increase from baseline (BL) by≥1.0 g/dL in any subject with BL Hb>8.0 g/dL, OR
	• an increase from BL by ≥2.0 g/dL in any subject with BL Hb ≤8.0 g/dL
	at two consecutive visits [dates] (with available data) separated by at least 5 days during the first 24 weeks of treatment without rescue therapy (i.e., red blood cell [RBC] transfusion, ESA, or intravenous [IV] iron) prior to Hb response.
Intervention	The drug, device, therapy or process under investigation in a clinical trial which has an effect on outcome of interest in a study: e.g., health-related quality of life, efficacy, safety, pharmacoeconomics.

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Terms	Definition of terms
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test drug or placebo (sometimes without randomization) is usually given to a subject, and continues until the last assessment after completing administration of the test drug or placebo.
Post study follow-up	Period of time from EOS visit to projected week 108 or until the last subject randomized reaches EOS, whichever comes first. This period is only applicable to subjects who discontinued treatment. These subjects will be followed up on a 6-monthly frequency for vital status and hospitalizations.
Primary treatment period	Period of time that subject is treated from first treatment up to 52 weeks
Pre-investigational period	Period of time before entering the investigational period, from the time of starting a subject enrolling into study until just before the test drug or comparative drug is given to a subject
Randomization	Action to allocate a subject to the treatment group or treatment cohort. Subjects will be randomized to roxadustat or placebo at day 1.
Roxadustat	International Nonproprietary Name (INN) of ASP1517/FG-4592 investigational product
Rescreening	Process of repeating screening. If a subject fails screening they may be rescreened once if deemed appropriate; all screening procedures will be repeated. Renal ultrasound only to be repeated if not within 12 weeks prior to randomization.
Rescreening failure	Subject who is rescreened, but did not fulfill protocol inclusion and/or exclusion criteria for a second time and failed to receive randomized treatment, or decided not to participate anymore (withdrew consent) prior to the treatment period.
Safety Emergent Period	Defined as the evaluation period from the Analysis date of first drug intake up to 28 days after the Analysis Last Dose
Screening	1) Process for retrieving candidates for the study. 2) Process for checking the eligibility of subjects usually done during the "pre-investigational period"
Screening failure	Screened subject, but did not fulfill protocol inclusion and/or exclusion criteria and failed to receive randomized treatment, or decided not to participate anymore (withdrew consent) prior to the treatment period.
Screening Hb value	Mean of subject's three last Hb valued collected during the screening period and prior to the day of randomization.
Serious Adverse Event	An adverse event is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: results in death, is life threatening, results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions, results in congenital anomaly, or birth defect, requires in-subject hospitalization or leads to prolongation of hospitalization, or a medically important event.

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Terms	Definition of terms
Study period	Period of time from first subject screened to end of the last scheduled visit of the last subject randomized
Subject	An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.
Time to event	Time from a defined starting point (analysis date of first dose intake) to the time of occurrence of the event of interest.
Time to censoring	Time from a defined starting point (analysis date of first dose intake) to the time of end of observation period in case the event did not occur.
Time to event analysis	Time to event analyses are statistical methods, such as survival analysis, that take into account 2 types of timing: the time to occurrence of an event (if an event occurred) and the time to censoring (if an event did not occur during the time we observed the subject). For time to censoring, we only know the total number of days in which the event didn't occur until the subject ceased to be followed (censored).
Treatment Period	Period of time from first study drug intake until last study drug intake. Minimum 52 weeks to a maximum of 104 weeks or until the last subject randomized to treatment has completed 40 weeks of treatment (or at the forecasted week 40 date if this subject discontinues treatment early)
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

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1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data.

The SAP is finalized and signed prior to any of the following: study unblinding, database hard lock, interim analysis, or accumulation of substantial amount of data in an open-label study to ensure lack of bias. For operational efficiency an earlier time is usually targeted and wherever possible, the SAP should be developed in parallel with protocol finalization. If the expected interval between First Subject In (FSI) and soft-lock is less than 12 weeks, then the SAP should be approved by 12 weeks prior to the planned date of soft-lock. If needed, revisions to the approved SAP may be made prior to database hard lock. Revisions will be version controlled.

This statistical analysis is coordinated by the responsible biostatistician of APEB. Any changes from the analyses planned in the SAP will be justified in the Clinical Study Report (CSR).

All details of the Pharmacokinetics Analysis Set (PKAS)_will be described in a separate analysis plan, and a separate PKAS modeling report will be written.

This SAP is based on protocol version 2.0, dated 17 December 2014 and on Case Report Form (CRF) version 17.0, dated 26 April 2017.

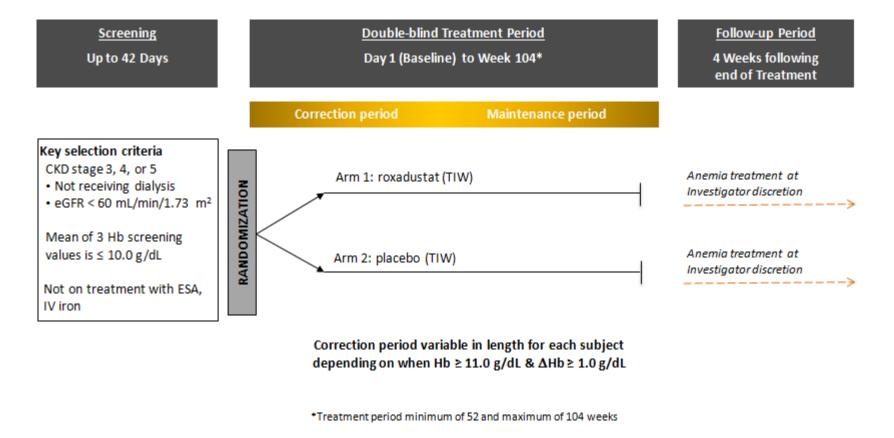
Prior to database hard lock, a final review of data and TLFs meeting will be held to allow a review of the clinical trial data and to verify the data that will be used for analysis set classification. If required, consequences for the statistical analysis will be discussed and documented. A meeting to determine analysis set classifications may also be held prior to database hard lock.

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2 FLOW CHART AND VISIT SCHEDULE

Flow Chart



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 Table 1
 Schedule of Assessments

Study Period:	: Screening		Screening Treatment ^a				Follow-up				Post study Follow- up	
	Up t	Up to 6 Weeks								EOS	-	
Visit / Week:	S1	S2	S3	Day 1 ^b	Weekly (wks 1 to 2) ± 2 days	Every 2 Weeks (wks 4 to 24) ± 2 days	Every 4 Weeks (wks 28 to 100) ± 3 days	EOT (wk 104) ± 3 days	EOT + 2 wks ± 3 days	(EOT + 4 wks) ± 3 days	Unscheduled Visits	Every 6 months until projected wk 108
Written informed consent	X				-							
Randomization				X								
Eligibility criteria	X			X								
Demographics and medical history including tobacco use	X											
Weight	X			X		wks 12, 24	wks 36, 52, 76	X		X	O^d	
Physical examination	X			X		wks 12° 24°	wks 36°, 52°, 76°	X		X ^c	O ^{c, d}	
Blood pressure ^e , heart rate ^e , respiratory rate ^g	X	X	X	X	X	X	X	X		X	X	
CBC with WBC differential, red cell indices and platelet count	X			X	X	wks 4, 8, 12, 20	wks	X		X	O _q	
Reticulocyte count, Hemoglobin content of reticulocytes (CHr)	X			X	X	wks 4, 6, 8, 12, 16, 20	wk 28 and every following 8 wks	X		X	O _q	
Hemoglobin ^h		X	X			X	X		X		X	
HemoCue® assessment i				X	X	X	X				X	
Serum chemistry (incl LFT)	X			X		wks 4, 8, 12, 20	wk 28 and every following 8 wks	X	X	X	O^d	
LFTs ^j					wk 2	wks 6, 16					O^d	
Serum Lipid panel (fasting whenever possible)	X			X		wks 4, 8, 12, 20	wks 28, 36, 44, 52, 68, 84	X		X	O ^d	
Serum iron, ferritin, TIBC, TSAT	X			X		wks 4, 8, 12, 20	wk 28 and every following 8 wks	X		X	O^d	
HbA1c	X			X		wk 12	wks 28, 36, 44, 60, 84	X		X	O^d	
Vitamin B ₁₂ , folate	X											
HIV Immunoassay, HBsAg, anti-HCV antibody	X											

Table continued on next page

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Study Period:	l: Screening		ıg			Treatment ^a			Follow-up			Post study Follow- up		
	Up t	Up to 6 Weeks		Up to 6 Weeks								EOS	=	•
Visit / Week:		S2	S3	Day 1 ^b	Weekly (wks 1 to 2) ± 2 days	Every 2 Weeks (wks 4 to 24) ± 2 days	Every 4 Weeks (wks 28 to 100) ± 3 days	EOT (wk 104) ± 3 days	EOT + 2 wks ± 3 days	(EOT + 4 wks) ± 3 days	Unscheduled Visits	Every 6 months until projected wk 108		
Serum Pregnancy test ^k	X					wks 12, 24	wks 36, 48, 60, 72, 84, 96	X			O^d			
eGFR (Cr Clear Modified Diet Abbreviated) ¹	X			X		wk 20	wks 36, 52, 68, 84	X		X	Od			
Special laboratory analytes (hepcidin, sTfR, hs-CRP)				X		wks 4, 12, 20	wks 36, 52	X		X				
Archival serum/plasma samples for biomarkers				X		wks 4, 12, 20	wks 52, 76	X		X				
Blood sample for population PK					wks	2 to 8 ^m								
Genotyping ⁿ						X								
Urinary testing ^o				X		wks 12, 24	wks 36, 52, 64, 76, 88				O^d			
Quality of Life Questionnaires p				X		wks 8, 12, 28	wks 36, 52, 76	X			O_q			
12-lead ECG	X			X		wks 12, 24	wks 36, 52, 76	X			O_q			
Renal ultrasound ^q		X									O^d			
Dose adjustment review ^r						X	X				O^d			
Hospitalization recording ^s	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse event recording	X	X	X	X	X	X	X	X	X	X	X			
Concomitant medication recording	X	X	X	X	X	X	X	X	X	X	X			
Procedure and non-drug therapy recording	X	X	X	X	X	X	X	X	X	X	X			
Study drug dispensing ^t				X ^u	X	X	X				O^d			
Vital Status, SAEs, cardiovascular and thromboembolic AEs							1(a) V					X		

S1/S2/S3 = screening visit 1, 2 and 3; EOT = End of Treatment; EOS = End of Study; wk(s) = week(s); X = mandatory test/assessment; O = optional test/assessment; see below for footnotes)

<u>Note</u>: see Appendix 3 from Protocol: Instructions for Subjects Moving from Protocol v1.0 to Protocol v2.0

Note: see Appendix 4 from Protocol: Instructions for Subjects Requiring Dialysis

 $Table\ footnotes\ continued\ on\ next\ page$

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- ^a In case of premature discontinuation or withdrawal during the treatment period, the subject should complete the EOT and EOS visits. Thereafter, this subject will continue to be followed up at a 6-monthly frequency for vital status and hospitalizations until their projected date of completion (i.e., projected week 108 date) or, if earlier, until the last subject randomized reaches EOS, or until consent withdrawn.
- ^b All study assessments to be performed prior to first study drug administration
- ^c Targeted physical examination only (e.g., respiratory and cardiovascular).
- ^d The study drug dosing is to be reviewed and if needed new or additional study drug is to be dispensed.
- ^e Blood pressure (BP) measured singly during the screening period, and in triplicate at all other visits. It is recommended during the treatment period, blood pressure measurement should occur prior to study drug administration if study medication is taken on same day of visit; except for visits where subjects are instructed to take study medication at home for PK sampling purpose. For subjects requiring dialysis, BP will be recorded prior to, and after dialysis (hemodiafiltration [HDF] subjects only).
- f Heart rate measured singly during the screening period, and in triplicate at all other visits. It is recommended during the treatment period, heart rate measurement should occur prior to study drug administration if study medication is taken on the same day of visit; except for visits where subjects are instructed to take study medication at home for PK sampling purposes. For subjects requiring dialysis, HR will be recorded prior to, and after dialysis (HD/HDF subjects only).
- Respiratory rate measured singly during all visit. It is recommended during the treatment period, respiratory rate measurement should occur prior to study drug administration except for visits where subjects are instructed to take study medication at home for PK sampling purposes. For subjects requiring dialysis, respiratory rate will be recorded prior to dialysis (HD/HDF subjects only).
- ^h Hemoglobin (Hb) should be collected at all the visits where complete Blood Count (CBC) is not collected
- ¹ Hb will be assessed by HemoCue on the blood sample, collected for Central Laboratory hemoglobin assessment
- ^j Liver Function Tests (LFTs) to be collected at visits where full Serum Chemistry is not collected
- ^k Collect from female subjects of child bearing potential only.
- ¹ Calculated by the Central Laboratory.
- ^m Sampling roxadustat will be done at 6 time points over 1 to 3 visits. See Section 5.6 from Protocol. At each pharmacokinetic visit, an additional sample will be collected for albumin and alpha-acid glycoprotein determination.
- ⁿ Optional assessment. A separate informed consent form must be signed before genotyping sample is collected. Sample collection can be done at any timepoint thought the treatment period of the study.
- ^o Ideally, the sample should be from the first morning void. Urinary testing includes qualitative testing with dipstick testing (for protein, pH, glucose) and quantitative assessment of albumin and creatinine for calculation of albumin/creatinine ratio. At day 1, weeks 24, 52 and 76 and EOT a urine sample will be archived for potential future biomarker analysis.
- ^p Quality of Life (QoL) Questionnaires used are SF-36, FACT-An, EQ-5D 5L, PGIC and WPAI:ANS. The PGIC questionnaire is not completed at Day 1. Questionnaires to be completed by the subject preferably prior to any study assessments. When subjects need dialysis therapy, QoL questionnaires will be completed on the day of first dialysis (preferably before the dialysis is started), 4 weeks later and 12 weeks later.
- ^q Renal ultrasound examination within 12 weeks of randomization. Not required if result of a previous renal ultrasound (or other imaging modality such as CT scan or MRI) within 12 weeks prior to randomization is available and rules out renal cell carcinoma. If other imaging modality, a conclusive report on the kidney should be available.
- ^r Dose adjustment review from week 4 onward, and every 4 weeks thereafter until EOT (except in the event of excessive hematopoiesis or Hb ≥13.0 g/dL). If next dose adjustment interval falls on a non-visit study week, the dose adjustment review should be performed at the next scheduled visit.
- ^s Telephone or in-person follow-up call with subject
- ^t For subjects requiring dialysis, it is recommended for HD/HDF subjects that study drug is administered any time after completion of dialysis (if dosing is scheduled on a dialysis day).
- ^u Intake of initial study drug on day of randomization.

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3 STUDY OBJECTIVES AND DESIGN

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of roxadustat in the treatment of anemia in non-dialysis CKD subjects.

3.1.2 Secondary Objectives

The secondary objectives in this study are to:

- Evaluate the safety of roxadustat in the treatment of anemia in non-dialysis CKD subjects.
- Evaluate HRQoL benefit of roxadustat treatment in subjects with non-dialysis CKD anemia.
- Evaluate the need for anemia rescue therapy with roxadustat in subjects with non-dialysis CKD anemia: RBC transfusion, ESA, or IV iron.

3.2 Study Design

3.2.1 General

This is a phase 3, multi-center, randomized, double-blind, placebo controlled study in anemic subjects with Stage 3, 4 or 5 CKD who are not on dialysis. This study is planned to recruit subjects from approximately 200 study centers, globally.

The study is planned to provide key efficacy and safety data for the approval of roxadustat in the treatment of anemia associated with CKD. Study FGCL-4592-060 with similar design is conducted by FibroGen Inc, in study centers across North America, Latin America and Asia Pacific.

3.2.2 Study Population

The study population consists of subjects with CKD stages 3, 4, and 5 (eGFR < 60 mL/min/1.73 m²) who are anemic and not on dialysis. Anemia is defined by mean Hb \leq 10.0 g/dL upon repeated screening measurements. Subjects do not need to be iron replete at BL; inclusion is permitted if ferritin \geq 30 ng/mL (\geq 67.4 pmol/L) and Transferrin Saturation (TSAT) \geq 5%. Anemia of non-renal origin is to be excluded. Washout periods of at least 12 weeks for any prior ESA or IV iron treatment or at least 8 weeks for any RBC transfusion prior to randomization have been mandated in order to exclude a potential impact of these extraneous anemia treatments on the assessment of efficacy.

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3.2.3 Description of Study

Subjects will take roxadustat or placebo orally as a combination of tablets of different strengths. All tablets for subjects receiving roxadustat will contain active ingredient whereas all tablets for subjects receiving placebo will contain just placebo. The study will consist of three study periods as follows:

- Screening period: up to 6 weeks.
- Treatment period: minimum 52 weeks (primary treatment period) up to a maximum of 104 weeks (extended treatment period) or until the last subject randomized to treatment has completed 40 weeks of treatment (or at the forecasted week 40 date if this subject discontinues treatment early). Treatment period for last patient randomized is 52 weeks.
- Post-treatment follow-up period: 4 weeks.
- Study termination and post-study follow-up period

During the course of the study, visits and assessments will be performed as defined in the Schedule of Assessments.

Subjects that have discontinued treatment prior to their projected week 104 will continue to be followed for vital status and hospitalizations in post study follow up.

Screening Period

During the screening period, subjects' eligibility for study participation will be assessed.

Treatment Period

The initial protocol Version 1.0 included a random allocation to 6 treatment arms in a 2:2:2:2:1:11 ratio. These 6 arms included placebo or roxadustat as double-blind treatment in a 2:1 ratio and each of these had 3 different dosing frequencies for the maintenance period. (TIW, BIW or QW). Following FDA's recommendation, the protocol was amended with the removal of the dosing frequencies BIW and QW and keeping only the TIW dosing frequency. This SAP is based on protocol version 2.0 using the pooled placebo and pooled roxadustat arms as treatment groups for comparison.

After subjects have been confirmed eligible for study participation, they will be randomized to receive 1 of 2 treatment arms. The randomization will result in a 2:1 ratio of subjects receiving roxadustat or placebo, respectively.

The initial study drug dose (per dose amount) is based on a tiered, weight-based dosing scheme shown in Table 2

Table 2 Initial Study Drug (Roxadustat/ Placebo) Dosing

Study Drug (Dose Frequency)	Weight $(\geq 45 \text{ to } \leq 70 \text{ kg})$	Weight $(>70 \text{ to} \le 160 \text{ kg})$
Roxadustat/Placebo (TIW)	70 mg	100 mg

Study drug will be dosed initially for Hb correction, until subjects achieve central Hb value of ≥ 11.0 g/dL and Hb increase from BL of ≥ 1.0 g/dL at two consecutive study visits separated by at least 5 days (correction period).

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Once Hb correction is reached the subject will enter the maintenance period. The aim of the maintenance period is to treat to a Hb level of 11.0 g/dL by maintaining the Hb levels between 10.0 g/dL and 12.0 g/dL. During the treatment period, subjects will attend weekly study visits from day 1 to week 2, followed by every other week study visits from weeks 4 to 24 and thereafter every four weeks until the end of treatment. Subjects will be treated with roxadustat or placebo for at least 52 weeks and will continue taking the double-blind treatment as they were assigned until a maximum of 104 weeks. Depending on the rate of recruitment, the maximum treatment period will be 104 weeks for subjects who were randomized early into the study.

- The last subject randomized will stop treatment at the minimum of 52 weeks.
- When the last subject randomized reaches 40 weeks of treatment (or the forecasted week 40 date, if the last subject randomized discontinues treatment early)
 - Subjects beyond 52 weeks treatment will stop treatment at this point.
 - Subjects that have not yet reached 52 weeks treatment will continue until they reach 52 weeks treatment.

For details on study drug dosing, see Protocol, Section 5.1.

Follow-up Period

After the Treatment period, subjects proceed to the 4-week post-treatment follow-up period.

Post Study Follow-up (only for subjects prematurely discontinued from treatment)

Subjects that have stopped treatment prior to their projected week 104 will complete the EOT visit and EOS visit. Thereafter, these subjects will continue to be followed up on a 6-monthly frequency for vital status and hospitalizations until their projected date of completion (i.e., projected week 108 date) or, if earlier, until the last subject randomized reaches EOS, or until consent withdrawn.

3.2.4 Comparator

Placebo has been chosen as comparator to adequately assess the efficacy, safety and benefit of achieving Hb correction and maintenance in anemic subjects treated with roxadustat. Scientifically, efficacy and benefit of a new investigational medicinal product is most convincingly established by demonstrating superiority in a placebo-controlled trial.

3.3 Randomization

A randomized double-blind design has been chosen in order to ensure a balanced allocation of study subjects to the treatment arms and to minimize bias in therapeutic management and in outcomes assessment.

Randomization and treatment assignments will be performed via Interactive Response Technology (IRT) prepared on behalf of the Sponsor (under the responsibility of the Data Science (DS) Department of APEB). Specific procedures for randomization through the IRS are contained in the study procedures manual.

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A total of 450-600 planned subjects will be randomized to receive one of the 2 treatment arms in a 2:1 ratio as follows:

- Roxadustat (planned 300-400 subjects)
- Placebo (planned 150-200 subjects)

Randomization will be stratified by the following four factors:

- Region (region A versus region B)*
 * assignment to region (see Section 6.5.2) will be determined based on health care system comparability.
- Screening Hb values ($\leq 8.0 \text{ g/dL versus} > 8.0 \text{ g/dL}$)
- History of cardiovascular, cerebrovascular or thromboembolic diseases (Yes versus No).
- eGFR ($< 30 \text{ mL/min}/1.73 \text{ m2 versus} \ge 30 \text{ mL/min}/1.73 \text{ m2}$).

Subjects randomized to roxadustat QW, BIW or TIW prior to implementation of protocol v2.0 will be pooled together. Subjects randomized to placebo will also be pooled together.

4 SAMPLE SIZE

A minimum of 450 and up to 600 subjects are planned to be randomized to receive roxadustat or placebo (2:1 with approximately 300 roxadustat versus 150 placebo) in a double-blind manner in order to support the primary endpoint(s) of the study.

EU (EMA)

Three hundred subjects for the roxadustat treatment group and 150 subjects for the placebo treatment group are needed to achieve at least power of 95% to demonstrate a statistically significant difference with a 5% two-sided significance level between roxadustat and placebo in the primary endpoint assuming that the proportion of subjects with response in the roxadustat group is at least 65% and in the placebo group is at most 25%.

USA (FDA)

A sample size of 450 will allow the study to have at least power of 99% to detect a 1.0 g/dL difference in mean Hb values between the two treatment groups, assuming that the common standard deviation is 1.2 g/dL using an analysis of variance (ANOVA) test with a 5% two-sided significance level.

Most importantly, this sample size is required for a meta-analysis of composite safety endpoint by pooling studies. In case the minimum size of four hundred and fifty subjects is not large enough to achieve the required number of MACE/MACE+ events, an increase in the sample size up to 600 is regarded.

5 ANALYSIS SETS

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9, the analysis sets below will be used for the analyses.

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Detailed criteria for analysis sets will be laid out in Classification Specifications (CS) and the allocation of subjects to analysis sets will be determined prior to database hard lock.

5.1 All Randomized

The All Randomized consists of all randomized subjects.

Criterion for exclusion from All Randomized is defined as follows:

Not randomized

The selection of subjects for the All Randomized will be confirmed in the Analysis Set Classification (ASC) meeting.

The All Randomized will be used for summaries, selected primary and secondary analyses of efficacy endpoints, as well as selected demographic and baseline characteristics.

The All Randomized Set will exclude the 3 subjects from site 70051, which has been terminated prematurely due to GCP violations including data integrity issues. Consequently, these subjects will not be included in any of the analyses.

5.2 Full Analysis Set (FAS)

The Full Analysis Set (FAS) consists of all randomized subjects who received at least one dose of study drug and have at least one non-missing post-dose Hb assessment. Subjects will be assigned to their planned treatment provided by the IRS.

Criteria for FAS exclusion is defined as follows:

- No study drug taken, or
- No Hb value post-dose

The selection of subjects for the FAS will be confirmed in the Analysis Set Classification (ASC) meeting.

The FAS will be used for summaries, selected primary and secondary analyses of efficacy endpoints, as well as selected demographic and baseline characteristics.

5.3 Per Protocol Set (PPS)

The Per-Protocol Set includes all FAS subjects who do not meet any of the reasons to exclude a complete subject from PPS listed in Table 3 This PPS will be used for all disposition, demography and baseline characteristics.

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Table 3 Criteria for excluding a subject from PPS

Number	Reasons for exclusion from PPS
1	Subject who receives less than 2 weeks of study treatment.
2	Patient without a valid corresponding Hb. A valid corresponding Hb is defined as an Hb value from the central laboratory that is measured at least 2 weeks after the first dose and was either before the last study drug intake or at maximum three days after the last drug intake.
3	Prescribed study drug compliance during treatment < 75% during the first 24 weeks or until EOT, whatever comes first.
4	Violation of inclusion or exclusion criteria which may affect the assessment of the efficacy of the study drug during the reference period or until EOT, whatever comes first.
5	Subjects where breaking of the randomization code occurs during the reference period or until EOT, whatever comes first.
6	Administration of wrong randomization study drug for more than one week during the reference period or until EOT, whatever comes first
7	Administration of prohibited concomitant medication affecting efficacy listed in Appendix 12.1 of the protocol during the first 24 weeks or until EOT, whatever comes first.
8	Administration of rescue therapy significantly deviating from the protocol during the first 24 weeks or until EOT, whatever comes first.

More information on the derivation of these criteria can be found in the Classification Specifications.

5.4 Safety Analysis Set (SAF)

The safety analysis set consists of all randomized subjects who received at least one dose of study drug. Subjects will be assigned to their actual treatment received during the trial.

The SAF will be used to describe demographic and baseline characteristics and all safety and tolerability related variables.

5.5 Pharmacokinetics Analysis Set (PKAS)

The PKAS includes the subjects from the SAF population who meet the following criteria:

- Received at least one dose of roxadustat
- At least one quantifiable plasma concentration of roxadustat was obtained; dosing and sampling history has been recorded.

PKAS will be defined separately and all analyses will be reported in a separate report.

5.6 Pharmacodynamic Analysis Set (PDAS)

Not applicable in this study.

6 ANALYSIS VARIABLES

6.1 Efficacy Endpoints

The **Efficacy Emergent Period** will be defined as the evaluation period from the Analysis date of first dose intake up to 7 days after the Analysis date of Last Dose (defined in Section 6.5.4) or EOT Visit, whichever occurs first. This period will be used as reference

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period for the time to event analyses related to efficacy endpoints, unless specified otherwise. More details on the derivation of the date of End of Efficacy Emergent Period are provided in Section 7.11.6

6.1.1 Primary Efficacy Endpoint

There are two separate regionally based primary efficacy endpoints in this study depending upon whether the data are being filed to support submission to the EU EMA or to ex-EU health authorities, such as the US FDA.

6.1.1.1 Primary Efficacy Endpoint for EU (EMA)

The primary efficacy endpoint is a binary variable, Hb response (Yes/No), where Yes is defined as:

- Hb \geq 11.0 g/dL and Hb increase from baseline by \geq 1.0 g/dL, for subjects with baseline Hb > 8.0 g/dL; or
- Hb increase from baseline by $\geq 2.0 \text{ g/dL}$, for subjects with baseline Hb $\leq 8.0 \text{ g/dL}$

at two consecutive visits [dates] (with available data) separated at least 5 days during the first 24 weeks of treatment without having received rescue therapy (RBC transfusion, ESA, or IV iron) prior to Hb response.

Both scheduled and unscheduled Hb values from the central laboratory will be taken into account.

The first date of the two consecutive visits will be used as the date of response. Analysis visits will be used to define the week of response (see Table 31 Section 7.11.4).

Subjects who discontinued or received rescue therapy prior to the first Hb that fulfills the definition of response or before the second consecutive Hb value that fulfills the definition of response, will be classified as non-responders.

Baseline Hb is defined as the mean of four central laboratory Hb values: four latest Hb values prior or on the same date as first study drug intake (pre-dose).

Definition of rescue therapy is provided in Section 6.1.2.3

6.1.1.2 Primary Efficacy Endpoint for US (FDA)

Hb change from baseline (BL) to the average Hb of weeks 28 to 52 regardless of rescue therapy.

The central laboratory reported Hb values will be used for this analysis.

All available Hb values obtained from the central laboratory will be used (i.e., both scheduled and unscheduled Hb values). Hb values in analysis visit windows at weeks 28, 32, 36, 40, 44, 48 and 52 will be used for the calculation of the average of weeks 28 to 52 (see Table 31 and Section 7.11.4 for the analysis windows definition and the differentiation between the MMRM and ANCOVA analyses).

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In case a subject does not have any available Hb value within this evaluation period refer to Section 7.11.1 for imputation rules.

Baseline Hb is defined as the mean of four central laboratory Hb values: four latest Hb values prior or on the same date as first study drug intake.

6.1.2 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints in this study are listed in Table 4

Table 4 Key Secondary Efficacy Endpoints

Number	Endpoint
1	Hb change from BL to the average Hb in weeks 28-36, without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period.
2	Change from BL in Low Density Lipoprotein (LDL) cholesterol to the average LDL cholesterol of weeks 12 to 28.
3	Occurrence and time to first use of rescue therapy [composite of RBC transfusions, IV iron supplementation and rescue ESA]
4	Change from BL in SF-36 Vitality (VT) sub-score to the average VT sub-score of weeks 12 to 28.
5	Change from BL in SF-36 Physical Functioning (PF) sub-score to the average PF sub-score of weeks 12 to 28.
6*	Change from BL in mean arterial pressure (MAP) to the average MAP value of weeks 20 to 28.
7*	Occurrence and time to first occurrence of hypertension (defined as either SBP \geq 170 mmHg AND an increase from BL \geq 20 mmHg or as DBP \geq 110 mmHg, AND an increase from BL of \geq 15 mmHg
8*	Rate of progression of CKD measured by annualized eGFR slope over time

^{*:} These key secondary endpoints will not be included in the hierarchical testing procedure.

6.1.2.1 Hb change from BL to the average Hb in weeks 28-36, without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period

All available Hb values obtained from the central laboratory will be used (i.e., both scheduled and unscheduled Hb values). Hb values in analysis visit windows at weeks 28, 32 and 36 will be used for the calculation of the average of weeks 28 to 36 (see Table 31 and Section 7.11.4 for the analysis windows definition and the differentiation between the MMRM and ANCOVA analyses).

In case a subject does not have any available Hb value within this evaluation period, or in case a subject requires rescue therapy within 6 weeks prior to and during this 8-week evaluation period, refer to Section 7.11.1 for imputation rules.

Baseline Hb is defined in Section 6.1.1.1

6.1.2.2 Change from BL in Low Density Lipoprotein (LDL) Cholesterol to the Average LDL Cholesterol of Weeks 12 to 28

The analysis will be done on all values (fasted and non fasted) of Day 1 and weeks 12 to 28.

All available LDL values will be used (regardless the fasting status), i.e., both scheduled and unscheduled LDL values. LDL values in analysis visit windows at weeks 12, 20 and 28 will

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be selected for the calculation of the average LDL cholesterol of weeks 12-28 (see <u>Table 33</u> and Section 7.11.4 for the analysis windows definition and the differentiation between the MMRM and ANCOVA analyses).

For missing LDL imputation rules, refer to Section 7.11.1 Baseline LDL is defined as the LDL value on Day 1. If this value is missing, the latest value prior to first study drug administration will be used.

This analysis will also be repeated for fasted values only as a sensitivity analysis.

6.1.2.3 Use and time to first use of rescue therapy (composite of RBC transfusions, ESA use, and IV iron)

RBC transfusion is collected in the Blood Transfusions form of the eCRF. The use of ESAs and IV iron is collected in the Concomitant Medication form of the eCRF (entries where "Given as Anemia Therapy?" is ticked). These medications will be coded into the ATC and WHO-DRL dictionaries.

The following WHO-DRL codes will be classified as ESA: '00909301001', '00928301001', '02198701001', '07973701001', '01703101001'. The following WHO-DRL code where route is INTRAVENOUS will be classified as IV IRON: '00023501001' and '90135401001'. The following WHO-DRL code will be classified as RBC transfusion: '01186901001'.

Only rescue medication that started during the study treatment and up to the end of Efficacy Emergent Period will be taken into account and considered as use of rescue. Medication started at End of Treatment visit will not be considered rescue for patients completed the treatment. Medication Onset Date is the date of the first use of rescue medication.

For a subject with use of rescue therapy, the time to use of rescue therapy will be calculated (in years) as:

(First event date – Analysis date of first dose intake + 1) / 365.25

With 'First event date' defined as 'Date of first dose of rescue medication' during the Efficacy Emergent Period and 'Analysis date of first dose intake' defined in Section 6.5.4

For a subject without use of rescue therapy, the time to censoring is calculated as:

[(Date of End of Efficacy Emergent Period – Analysis date of first dose intake + 1] / 365.25 With date of End of Efficacy Emergent Period defined in Section 7.11.6

6.1.2.4 Change from BL in SF-36 Vitality (VT) Sub-score to the Average VT Sub-score of Weeks 12 to 28

For details on the calculation of the SF-36 VT scale subscore, see Section 6.1.3.14.1

All available SF-36 VT values will be used i.e., both scheduled and unscheduled SF-36 VT values. SF-36 PF values in analysis visit windows at weeks 12 and 28 will be selected for the calculation of the average VT sub-score of weeks 12 to 28 (see Table 32 and Section 7.11.4 for the analysis windows definition and the differentiation between the MMRM and ANCOVA analyses).

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For missing SF-36 VT, refer to Section 7.11.1 for the imputation rules. Baseline assessment is the assessment from Day 1 visit.

6.1.2.5 Change from BL in SF-36 Physical Functioning (PF) Sub-score to the Average PF Sub-score of Weeks 12 to 28

For details on the SF-36 PF subscore, refer to Section 6.1.3.14.1 Similar rules as for Section 6.1.2.4 will be used for the calculation of the SF-36 VT scale sub-score.

6.1.2.6 Change from BL in Mean Arterial Pressure (MAP) to the Average MAP Value of Weeks 20 to 28

Blood pressure will be measured singly for the three visits during the screening period and in triplicate with a 2-minute interval for all other visits during the study. During the study, for systolic blood pressure (SBP) and diastolic blood pressure (DBP), the average will be calculated for each visit using the three readings. If less than three readings are available, all will be used in the calculation of the average.

MAP will be derived for each visit from the above averaged SBP and the DBP using the following equation:

$$MAP = (2/3) * DBP + (1/3) * SBP$$

All available MAP values during the Safety Emergent Period will be used, i.e. both scheduled and unscheduled MAP values. MAP values in analysis visit windows at weeks 20, 22, 24 and 28 will be selected for the calculation of the average MAP during weeks 20-28 (see Table 31 and Section 7.11.4 for the analysis windows definition and the differentiation between the MMRM and ANCOVA analyses).

For missing data imputation rules, refer to Section 7.11.1 Baseline assessment is the assessment on Day 1 (average of the three readings). If the baseline assessment is missing, then the latest available value prior to first drug administration will be used.

6.1.2.7 Occurrence and time to first occurrence of hypertension

Occurrence of an increase in blood pressure is a binary variable (Yes/No), defined as:

- systolic blood pressure (SBP) increase from BL \geq 20 mmHg AND SBP \geq 170 mmHg, or
- diastolic blood pressure (DBP) increase from BL ≥15 mmHg AND DBP ≥110 mmHg.

The date of occurrence of hypertension is defined as the first date where SBP criterion or DBP criterion is met, whichever occurs first.

At each visit, SBP and DBP are calculated as the average from the 3 readings. If less than three readings are available, the non-missing readings will be used in the calculation of the average.

Baseline assessment is the assessment from Day 1. If this value is missing, then the latest available value from the screening period will be used.

Only events starting during the Safety Emergent Period (defined in Section 6.2) will be taken into account.

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The time to occurrence of hypertension for a subject with the event of interest will be calculated (in years) as:

(First event date – Analysis date of first dose intake + 1) / 365.25Where 'Analysis date of first dose intake' is defined in Section 6.5.4 and where 'First event date' is the first date of occurrence of hypertension. The time to censoring for a subject without the event of interest is calculated as: (Date of last vital signs assessment during the Safety Emergent Period – Analysis date of first dose intake + 1) / 365.25Refer to Sections 6.2 and 7.11.5 for more details regarding the Safety Emergent Period.

6.1.2.8 Rate of progression of CKD measured by annualized eGFR slope over time

Any eGFR values obtained from start of dialysis treatment (acute or chronic) will be excluded for the summaries and statistical analyses.

6.1.3 Additional Secondary Efficacy Endpoints

The additional secondary efficacy endpoints are listed in Table 5

Table 5 Additional Secondary Efficacy Endpoints

Table 3	Additional Secondary Efficacy Endpoints		
Number	Endpoint		
	Hb correction and maintenance		
1	Hb level averaged over weeks 28 to 36, 44 to 52, and 96 to 104 without use of rescue therapy within		
	6 weeks prior to and during this evaluation period.		
2	Time to achieve the first Hb response as defined by primary endpoint.		
3	Hb change from BL to each post-dosing time point.		
4	Hb change from BL to the average Hb value of weeks 28 to 36, 44 to 52, and 96 to 104 regardless		
	of the use of rescue therapy.		
5	Proportion of Hb values within 10.0 to 12.0 g/dL and ≥10.0 g/dL in weeks 28 to 36, 44 to 52, and 96		
	to 104 without use of rescue therapy within 6 weeks prior to and during these 8-week evaluation		
	periods.		
	Hospitalizations		
6	Occurrence (number) of hospitalizations, number of days of hospitalization per patient-year exposure		
	and time to first hospitalization.		
	Rescue Therapy Use		
7	Time to first use of rescue therapy (composite of RBC transfusions, ESA use, and IV iron) in the		
	first 24 weeks of treatment.		
8	Occurrence and time to first use of RBC transfusions, number of RBC packs per month subject,		
	volume of RBC transfused per month.		
9	Occurrence and time to first use of ESA. Number of ESA-Weeks per year		
10	Occurrence and time to first use of IV iron supplementation. Mean monthly IV iron (mg) per subject		
	during day 1 to week 36, weeks 37-52 and weeks 53-104 (monthly defined as a period of 4 weeks).		
	Change in Cholesterol Levels, Apolipoproteins		
11	Change from BL to each post-dosing study visit in Total cholesterol, LDL/High-density Lipoprotein		
	(HDL) ratio, Non-HDL cholesterol, Apolipoproteins A1 and B, ApoB/ApoA1 ratio.		
12	Occurrence of mean LDL cholesterol <100 mg/dL calculated over weeks 12 to 28.		
	Blood Pressure Effect		
13	Occurrence of achieved antihypertensive treatment goal in CKD subjects (SBP< 130 mmHg and		
	DBP< 80 mmHg) based on the mean SBP and mean DBP calculated over weeks 12 to 28.		
Table con	tinued on next page		

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Number	Endpoint
	HRQoL
14	Change from BL to the average value of weeks 12 to 28 (SF-36 Physical Component Score (PCS),
	Anemia Subscale ("Additional Concerns") of Functional Assessment of Cancer Therapy
	(FACT-An) Score, Total FACT-An Score, EQ-5D 5L VAS Score and Work Productivity and
	Activity Impairment (WPAI:ANS).
15	Patient Global Impression of Change (PGIC).
	Hepcidin, Iron status, HbA1c, and CKD progression
16	Changes from BL to each study visit (when measured) in Serum hepcidin, Serum ferritin, TSAT,
	HbA1c level, Fasting blood glucose, eGFR, Urine albumin/creatinine ratio, Time to (and proportion
	of subjects) Serum Creatinine having doubled during the study and Proportion of subjects with
	ESRD.

6.1.3.1 Hb level averaged over weeks 28 to 36, 44 to 52, and 96 to 104 without use of rescue therapy within 6 weeks prior to and during this evaluation period.

All scheduled and unscheduled hemoglobin values that belong to each period will be taken into account for calculating the average using the analysis windows (defined in Table 31 Section 7.11.4).

In addition, the averages over weeks 28-36, 44-52 and 96-104 will be categorized into the following categories:

- <10.0 g/dL,
- 10.0-12.0 g/dL,
- >12.0 g/dL,
- $\geq 10.0 \text{ g/dL}$.

In case a subject does not have any available Hb value within this evaluation period, or in case a subject requires rescue therapy within 6 weeks prior to and during this 8-week evaluation period, refer to Section 7.11.1 for imputation rules

6.1.3.2 Time to achieve the first Hb response as defined by primary endpoint.

6.1.3.2.1 Time (weeks) to achieve the first Hb response, without rescue therapy, as defined by the primary endpoint

Hb response is defined in Section 6.1.1.1

For a subject without rescue therapy before Hb response, the time to achieve Hb response will be calculated (in weeks) as:

(First event date – Analysis date of first dose intake + 1) / 7

where 'First event date' is defined as 'First date of both values that meet the criteria for response' and 'Analysis date of first dose intake' is defined in Section 6.5.4

For a subject without Hb response or with rescue therapy before Hb response, the time to censoring will be calculated (in weeks) as:

(Min[Date of End of Efficacy Emergent Period, Date of initiation of rescue therapy, Analysis date of Week 24 visit] – Analysis date of first dose intake+ 1) / 7

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6.1.3.3 Hb change from BL to each post-dosing time point

All scheduled and unscheduled hemoglobin values that belong to each window will be taken into account using one value per analysis window, as defined in Table 31 and Section 7.11.4

Baseline Hb is defined in Section 6.1.1.1

At each visit, Hb will also be categorized into the following categories: <10 g/dL, 10-12 g/dL and >12 g/dL.

6.1.3.4 Hb change from BL to the average Hb value of weeks 28 to 36, 44 to 52, and 96 to 104 regardless of the use of rescue therapy

The same rules as defined in Section 6.1.2.1, but regardless use of rescue therapy.

6.1.3.5 Categorical analysis of Hb values

The following endpoints will be analyzed: proportion of Hb values within 10.0-12.0 g/dL and \geq 10.0 g/dL, by time intervals, the percentage of time with Hb values falling in each Hb interval (< 10.0 g/dL, within 10.0-12.0 g/dL, \geq 10.0 g/dL, > 12.0 g/dL, > 13.0 g/dL and > 14.0 g/dL) during the Efficacy Emergent Period and the potential Excessive Hematopoiesis (EH).

Proportion of Hb values:

The following proportion in percentage for each subject will be defined:

Number of Hb values within 10.0-12.0 g/dL / Total number of Hb values*100 and (≥10.0 g/dL)/Total number of Hb values*100

in weeks 28 to 36, 44 to 52 and 96 to 104 without use of rescue therapy within 6 weeks prior to and during this 8 week evaluation period. All scheduled and unscheduled hemoglobin values that belong to each period will be taken into account using the analysis windows defined in Table 31, Section 7.11.4

Percentage of time

The percentage of time each patient has a Hb value <10.0 g/dL, within 10.0-12.0 g/dL, $\ge 10.0 \text{ g/dL}$, > 12.0 g/dL, > 13.0 g/dL or > 14.0 g/dL

will be calculated (as a percentage of the total of the length of time between the first and last Hb assessment during the evaluated period). The percentage of time will be calculated via linear interpolation. That is, if the change in Hb category (for instance from within 10.0-12.0 g/dL to > 12.0 g/dL) occurs between two visits V0 and V1, the day of change will be calculated by:

$$x = x_0 + (y - y_0) \frac{(x_1 - x_0)}{(y_1 - y_0)}$$

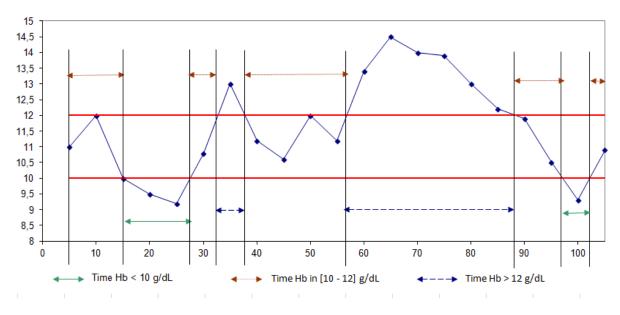
Where x_1 and x_0 are the dates when Hb was measured at V0 and V1 respectively, y_0 and y_1 are the Hb value at the respective visits V0 and V1 and y is the level of the Hb

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boundary (i.e 12.0, 13.0 or 14.0 g/dL). Percentage of time each subject has Hb value ≥ 10.0 g/dL will be derived as 100% - percentage time for Hb values ≤ 10 g/dL.

Figure 1 shows visually how the linear interpolation will calculate the total number of days that a subject is in each Hb category for an example subject:

Figure 1 Example of Linear Extrapolation



In case that several Hb values are on the same day the average of these values will be used to represent the Hb of that day in the above formula. This calculation will provide the day that the change in Hb value occurs. The number of days that the Hb value has been in each category will be determined and the percentage calculated based on the length of time between the first and last Hb assessment during the evaluated period, i.e.:

Date of Last Hb assessment during the evaluated period – Date of first assessment during the evaluated period.

No imputation will be performed if no Hb value is available in relevant time windows.

In case a subject requires rescue therapy within 6 weeks prior to and during these 8-week evaluation periods, refer to Section 7.11.1 for imputation rules.

Potential Excessive Hematopoiesis (EH), regardless use of rescue therapy, based on Hb central lab will be defined as:

 Hb increase by >2.0 g/dL between any two visits within 4 weeks of treatment during the Efficacy Emergent Period.

Time to first occurrence of potential EH regardless the use of rescue therapy during the Efficacy Emergent Period will be defined in weeks as:

(First event date – Analysis date of first dose intake + 1) / 7

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where 'First event date' is defined as first date of occurence of the criterion met during the Efficacy Emergent Period.

For a subject without potential EH, the time to censoring will be calculated (in weeks) as:

(Date of last hemoglobin assessment during the Efficacy Emergent Period – Analysis date of first dose intake + 1) / 7

Refer to Section 6.1 and 7.11.6 for the definition of the Efficacy Emergent Period.

6.1.3.6 Occurrence (number) of hospitalizations, number of days of hospitalization per patient- exposure -year and time to first hospitalization

The occurrence and the number of hospitalizations per subject during the Efficacy Emergent Period will be calculated.

The number of days of hospitalization per patient- exposure-year (PEY) will be calculated as:

[Sum of the durations of all hospitalizations in days (Minimum ((Date of discharge, End of Efficacy Emergent Period) – Date of admission + 1)] / [(Duration of Efficacy Emergent Period in days / 365.25)].

When hospitalization is ongoing, the date of end of the Efficacy Emergen Period will be used for the derivation of the hospitalization duration. In case of missing dates the hospitalization duration will be imputed by the average duration per stay derived from the subjects with non-missing duration within the same treatment group . Duration of treatment exposure is defined in Section 6.5.4

If the date of admission of a hospitalization record is the same as the date of discharge of the previous record, for example because two records are created to illustrate that the subject is moved from one hospital to another hospital or from a standard care to the intensive care unit (ICU), then the date of the transfer should not be counted twice and thus the hospitalizations duration for the later period is calculated as (Date of discharge – Date of admission). In such case hospitalization occurrence will also be counted only once.

Hospitalizations will also be described by reason for admission (admission for anemia or other reasons).

Time to first hospitalization in years will be defined in years as:

(First event date during the Efficacy Emergent Period – Analysis date of first dose intake + 1)/365.25

With 'First event date' defined as 'Date of first Admission' and 'Analysis date of first dose intake defined in Section 6.5.4

For a subject without hospitalization, the time to censoring will be calculated as:

[Date of End of Efficacy Emergent Period – Analysis date of first dose intake + 1) / 365.25

With date of End of Efficacy Emergent Period is defined in Section 7.11.6

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6.1.3.7 Occurrence and time to first use of rescue therapy [composite of RBC transfusions, IV iron supplementation and ESA treatment] during the first 24 weeks

Rescue medication is defined in Section 6.1.2.3 Start of rescue medication is only counted as event if it was started within the first 24 weeks of treatment. Subjects without event were censored at the date of the Week 24 visit.

6.1.3.8 Occurrence and time to first use of RBC transfusions, number of RBC packs per month, volume of RBC transfused per month

The blood transfusion form of the eCRF in the cumulative visit will be used to derive the number of RBC packs.

Monthly volume of blood transfused and the monthly total number of RBC units/packs (for each subject, the sum of blood volume and units transfused during the Efficacy Emergent Period / divided total number of days multiplied by 28 days) will be derived.

For RBC transfusions, when the number of units is not given but the volume transfused is given, the number of units will be estimated by volume transfused/250 mL (for transfusion of packed cell units) or volume transfused/500 mL (for transfusion of full blood).

When transfused volume is not given but the number of RBC units is given, the volume will be estimated as number of RBC units times 250 mL (for transfusion of packed cell units) or number of units times 500 mL (for transfusion of full blood).'

For subjects with use of RBC transfusion, the time to use of RBC transfusion is calculated as:

(First event date – Analysis date of first dose intake + 1) / 365.25

With 'First event date' defined as 'Date of first RBC transfusion' during the Efficacy Emergent Period and 'Analysis Date of first dose intake' defined in Section 6.5.4

For a subject without use of RBC transfusion, the time to censoring is calculated as:

(Date of End of Efficacy Emergent Period – Analysis date of first dose intake + 1] / 365.25

With date of End of Efficacy Emergent Period defined in Section 7.11.6

6.1.3.9 Occurrence and time to first use of IV iron supplementation. Mean monthly IV iron (mg) per subject during day 1 to week 36, weeks 37-52 and weeks 53-104 (monthly defined as a period of 4 weeks)

The use of IV iron is collected in the *Concomitant Medication* form of the eCRF. The route of administration (Intravenous) is also captured in the eCRF. All medications are coded with WHO-DD. Records selected will be those coded as IRON PREPARATIONS, ATC 3rd level code: B03A and where route is INTRAVENOUS.

Having received IV Iron is a binary variable (Yes/No), where "Yes" is defined as having at least one record selected during the Efficacy Emergent Period. The Efficacy Emergent Period will be divided in periods of 28 days and for each of these periods, the monthly mean of IV iron will be calculated.

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Only use of IV Iron that was ongoing or started during the Efficacy Emergent Period will be taken into account.

The Mean Monthly IV iron use per subject (in mg) during the first 36 weeks is defined by the following formula:

```
Total of IV iron use (mg) from Analysis date of first dose intake to Min(Analysis Date of Week 36 visit, Analysis date of last dose)
```

((Min(Analysis Date of Week 36 visit, Analysis date of last dose) - Day 1 Date) + 1)/28

Monthly is defined as a period of 4 weeks.

Subjects without a relevant concomitant medication record will be assumed that they used no IV iron, thus set to 0 mg.

The same method will be used to calculate monthly IV iron use for week 37-52 and 53-104. Analysis visits will be used as indicated in Section 7.11.4

For subjects with use of IV iron, the time to first use of IV iron is calculated as:

```
(First event date – Analysis date of first dose intake + 1) / 365.25
```

With 'First event date' defined as 'Date of first IV iron' during the Efficacy Emergent Period and 'Analysis date of first dose intake' defined in Section 6.5.4

For a subject without use of IV iron, the time to censoringis calculated as:

(Date of End of Efficacy Emergent Period – Analysis date of first dose intake + 1] / 365.25

With date of End of Efficacy Emergent Period defined in Section 7.11.6

6.1.3.10 Occurrence and time to first use of ESA. Number of ESA-Weeks per year

The concomitant medication form of the eCRF in the cumulative visit will be used to detect rescue medication with ESAs as defined in Section 6.1.2.3

The number of ESA-weeks per year are defined as the duration of ESA exposure divided by the total efficacy period in years. Each period when ESA [ATC code = B03XA] was taken will be summed by subjects as follows:

[sum (each period (min(End date of efficacy emergent period, End date of ESA therapy) + X days – Start date of ESA therapy +1)/7)]/total period in years;

X will be defined as the duration of the effect of ESA following the last ESA administration, based on the following rules:

```
If Frequency = 1 PER WEEK then X=7
```

If Frequency = 2 PER WEEK then X=3

If Frequency = 3 PER WEEK then X=2

If Frequency = 1 PER MONTH then X=28

If Frequency = ONCE then X=0

If Frequency = BIM (Bi-monthly) then X=14

If Frequency = QD (daily) then X=1

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If Frequency = QM (monthly) then X=28

If Frequency =QOD (every other day) then X=2

If Frequency = TID (three times daily) then X=1

If Frequency = 4 TIMES PER WEEK then X=2

If Frequency = EVERY 3 WEEKS then X=21

Additional frequency may be considered depending on the data.

For subjects with use of ESA, the time to first use of ESA is calculated as:

(First event date – Analysis date of first dose intake + 1) / 365.25

With 'First event date' defined as 'Date of first ESA' and 'Analysis date of first dose intake' defined in Section 6.5.4

For a subject without use of ESA, the time to censoring is calculated as:

(Date of End of Efficacy Emergent Period – Analysis date of first dose intake + 1] / 365.25

With date of End of Efficacy Emergent Period defined in Section 7.11.6

6.1.3.11 Change from BL to each post-dosing study visit in Total cholesterol, LDL/High-density Lipoprotein (HDL) ratio, Non-HDL cholesterol, Apolipoproteins A1 and B, ApoB/ApoA1 ratio

For each sample the following will be calculated:

- LDL/HDL ratio (LDL Cholesterol divided by HDL Cholesterol)
- Non-HDL cholesterol (Total Cholesterol minus HDL Cholesterol)

Change from baseline to each post-dosing study visit will be calculated for the following lipid parameters:

- Total cholesterol
- LDL cholesterol
- HDL cholesterol
- Low-density lipoprotein (LDL) / high-density lipoprotein (HDL) ratio
- Non-HDL cholesterol
- Triglyceride
- Apolipoproteins A1 and B (ApoA1 and ApoB)
- ApoB/ApoA1 ratio.

All available data will be summarized descriptively for all parameters above, regardless of fasting status.

No imputation will be performed in case of a missing value. If several values are available in the same window, one value will be used, as defined in Table 33 and Section 7.11.4

Baseline assessment is the assessment from Day 1 visit. If this value is missing, then the latest screening period value will be used as baseline.

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6.1.3.12 Occurrence of mean LDL cholesterol <100 mg/dL calculated over weeks 12 to 28

The evaluation period is defined as the average of all available LDL cholesterol values in weeks 12-28 (visit at 12, 20 and 28 weeks, as defined in Table 33 and Section 7.11.4). The occurrence of mean LDL cholesterol <100 mg/dL over weeks 12 to 28 will then be defined as a binary variable (Yes/No), where "Yes" is defined as mean LDL cholesterol <100 mg/dL over weeks 12 to 28.

No imputation will be performed in case of a missing value.

This endpoint will be reported on fasting values and regardless of fasting status.

6.1.3.13 Occurrence of achieved antihypertensive treatment goal in CKD subjects (SBP < 130 mmHg and DBP < 80 mmHg) based on the mean SBP and mean DBP calculated over weeks 12 to 28

Occurrence of achieved antihypertensive treatment goal (SBP < 130 mmHg and DBP < 80 mmHg) based on the mean SBP and mean DBP is calculated over an evaluation period defined as the average of all available values in weeks 12 to 28 during the Safety Emergent Period, similarly as in Section 6.1.2.6 (analysis windows defined in Table 31 Section 7.11.4). Occurrence of achieved antihypertensive treatment goal will then be defined as a binary variable (Yes/No), where "Yes" is defined as SBP < 130 mmHg and DBP < 80 mmHg.

No imputation will be performed in case of a missing value.

6.1.3.14 Change from BL to the average value of weeks 12 to 28 in Quality of Life scores

All study subjects will be required to complete Quality of Life (QoL) questionnaires as indicated in the schedule of assessments:

- SF-36
- FACT-An
- EQ-5D 5L
- WPAI:ANS

The next sections provide further details on how to derive these instruments, some derivations will be provided by an external vendor (QualityMetric).

6.1.3.14.1 Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)

The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) is a multi-purpose, short-form health survey with 36 questions (see Appendix 10.1). It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. Accordingly, the SF-36 has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments.

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The SF-36 contains 36 items that measure eight dimensions or scales: (1) physical functioning (PF); (2) role limitations due to physical health problems (RP); (3) bodily pain (BP); (4) social functioning (SF); (5) general health perceptions (GH); (6) role limitations due to emotional problems (RE); (7) vitality, energy or fatigue (VT); and (8) mental health (MH) (see Appendix 10.1). In addition, two summary measures, defined as the Physical Component Score (SF-36 PCS) and Mental Component Score (SF-36 MCS) will be provided.

Scoring of each dimension and the summary measure will be performed by QualyMetric using QualityMetric Health Outcomes(tm) Scoring Software 4.5.

Change from baseline to the average value in weeks 12-28 will be calculated for the Physical Component Scores of SF-36 (SF-36 PCS), following the same rules as defined in Section 6.1.2.5

For missing SF-36 PCS values, refer to Section 7.11.1 imputation rules. Baseline always refers to the assessment at day 1 to be performed prior to first study drug administration.

The number and percent of subjects with an increase from baseline of <3 />=3 points and of <5 />=5 points will be calculated for each visit for the following: Vitality Score (SF-36 VT), Physical Functioning score (SF-36 PF) and Physical Component score (SF-36 PCS).

In addition, the eight dimensions and the two summary measures and their associated change from baseline will be reported by visit.

6.1.3.14.2 Functional Assessment of Cancer Therapy – Anemia (FACT-An)

The Functional Assessment of Cancer Therapy – General (FACT-G; version 4) contains 27 items that cover four dimensions of well-being: physical (PWB) – 7 items, functional (FWB) – 7 items, social/family (SWB) – 7 items, and emotional (EWB) – 6 items.

The 'additional concerns' section contains 20 items: 13 fatigue specific items plus 7 additional items related to anemia were developed for use in conjunction with the FACT-G (Cella 1997). The 13 fatigue items plus the seven additional items related to anemia comprise the Anemia Subscale (AnS). Administration of the FACT-G plus the Anemia Subscale (AnS) is referred to as the FACT-An. The FACT-An has a recall period of the 'past seven days'. Respondents are asked to provide responses, (i.e., 'Not at all', 'A little bit', 'Somewhat', 'Quite a bit' and 'Very much'), to a list of statements which are either positively or negatively phrased. A final higher score indicates better QoL (see Appendix 10.2).

Each individual item is scored from 0 (Not at all) to 4 (Very much), and then the total score is obtained by summation of the resulted scores.

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If there are missing items, subscale scores can be standardized. This is done by multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items actually answered. This can be done on the scoring guide or by using the formula below:

Prorated subscale score = $[Sum of item scores] \times [N of items in subscale] / [N of items answered]$

When there are missing data, standardizing by subscale in this way is acceptable (Webster 2003) as long as more than 50% of the items were answered (e.g., a minimum of 4 of 7 items, 4 of 6 items, etc). The total score is then calculated as the sum of the un-weighted subscale scores. The FACT scale is considered to be an acceptable indicator of a subject's quality of life as long as overall item response rate is greater than 80% (e.g., at least 22 of 27 FACT-G items completed). This is not to be confused with individual subscale item response rate, which allows a subscale score to be prorated for missing items if greater than 50% of items are answered. In addition, a total score should only be calculated if ALL of the component subscales have available scores.

The FACT-An instrument will be scored according to Appendix 10.2 The following 9 scores will be calculated:

- PWB subscale score
- SWB subscale score
- EWB subscale score
- FWB subscale score
- AnS subscale score
- FACT-An TOI score
- FACT-G total score
- FACT-An total score
- Fatigue subscale score

Change from baseline to the average value in weeks 12-28 will be reported for the two scores (Anemia subscale 'Additional concerns' of FACT-An score and Total FACT-AN score). In addition, the score and change from baseline will be reported for each visit for all six scores.

Change from baseline to the average value in weeks 12-28 will be calculated for the FACT-An subscore, following the same rules as defined in Section 6.1.2.4

No imputation will be performed in case of a missing value.

Baseline always refers to the assessment at day 1 to be performed prior to first study drug administration.

6.1.3.14.3 EQ-5D 5L

The EQ-5D 5L is an international standardized non-disease specific (i.e., generic) instrument for describing and valuing health status, and a multi-dimensional measure of health-related QoL (see Appendix 10.3).

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It includes two main components: (1) a VAS scale rating perception of overall health and (2) 5 qualitative domains: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. For more details and description of the questionnaire, refer to Appendix 10.3

Change from baseline to the average value in weeks 12-28 will be calculated for the EQ 5D 5L VAS, following the same rules as defined in Section 6.1.2.4

Frequency distributions will be described for each visit for:

- EQ-5D 5L Mobility Score
- EQ-5D 5L Self-Care Score
- EQ-5D 5L Usual Activities Score
- EQ-5D 5L Pain/Discomfort Score
- EQ-5D 5L Anxiety/Depression Score

The evaluation period for the VAS score is defined as the average of available EQ-5D 5L VAS scores of weeks 12-28 (visit at W12 and W28).

No imputation will be performed in case of a missing item. Baseline always refers to the assessment at day 1 to be performed prior to first study drug administration.

6.1.3.14.4 Work Productivity and Activity Impairment (WPAI: ANS)

The objective of the Work Productivity and Activity Impairment questionnaire: Anemic Symptoms v2 (WPAI: ANS) is to measure work and activity impairment during the past seven days due to anemia. It is self-assessed. The WPAI: ANS consists of 6 questions, including asking if the subject is working, how many hours the person missed work due to anemic symptoms, how many hours the subject actually worked and how the anemic symptoms impacted the productivity and ability to do daily activities (see Appendix 10.4).

For subjects who are currently employed, the following four items will be calculated:

- Percent work time missed due to anaemic symptoms: 100 x Q2/(Q2+Q4)
- Percent impairment while working due to anaemic symptoms: 100 x Q5/10
- Percent overall work impairment due to anaemic symptoms: 100 x Q2/(Q2+Q4)+[(1-Q2/(Q2+Q4))x(Q5/10)]
- Percent activity impairment due to anaemic symptoms: 100 x Q6/10

Change from baseline to the average value in weeks 12-28 and in weeks 36-52 will be calculated for these items, following the same rules as defined in Section 6.1.2.4 The evaluation period score is defined as the average of available WPAI: ANS subscore of weeks 12-28 (visit at W12 and W28) and weeks 36-52 (visit at W36 and W52).

No imputation will be performed in case of a missing item. Baseline always refers to the assessment at day 1 to be performed prior to first study drug administration.

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6.1.3.15 Patients' Global Impression of Change (PGIC)

The Patients' Global Impression of Change (PGIC) is a subject-rated instrument that measures change in subjects' overall status since the start of the study on a 7-point qualitative scale ranging from 1 (very much improved) to 7 (very much worse) (see Appendix 10.5).

Data will be reported qualitatively by assessment as follows:

- Reported subject status,
- Combined Categories as binary:
 - Very Much Improved + Much Improved (yes/no)
 - Very Much Improved + Much Improved + Minimally Improved (yes/no)

No imputations will be performed in case of a missing item.

6.1.3.16 Hepcidin and Iron, HbA1c and CKD progression parameters

Changes from baseline to each study visit (see analysis windows in Table 31 Section 7.11.4) will be calculated for these parameters:

- 1. Serum hepcidin
- 2. Serum ferritin
- 3. Serum Iron
- 4. TSAT
- 5. HbA1c level
- 6. Fasting blood glucose
- 7. Serum creatinine (log transformed)
- 8. Albumin/creatinine ratio in urine (log transformed)

Serum creatinine and albumin/creatinine ratio in urine will be log transformed and any assessment occurring after the initiation of any dialysis (acute or chronic) will be excluded for the summaries.

For all variables above, baseline assessment is the assessment from Day 1 visit. If this value is missing, then the screening period value, if collected for that parameter, will be used.

CKD Progression variables:

• Time to CKD progression (composite of doubling serum creatinine, chronic dialysis or renal transplant, and Death)

First occurrence of serum creatinine being doubled compared with baseline during the Safety Emergent Period (see Section 6.2) will be calculated.

Occurrence of chronic dialysis or renal transplant (whichever occurring first) during the Safety Emergent Period (see Section 6.2) will be calculated.

Time to occurrence for a subject who died during the Safety Emergent Period (see Section 6.2) will be calculated.

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For a subject, the time to CKD progression will be calculated (in years) as:

(First event date – Analysis date of first dose intake + 1) / 365.25

With 'First event date' defined as 'First occurrence of serum creatinine being doubled compared with baseline, first occurrence of chronic dialysis or renal transplant, occurrence of subject who died (whichever occurring first)' and 'Analysis date of first dose intake' defined in Section 6.5.4

For a subject without event, the time to censoring will be calculated (in years) as:

(End of Safety Emergent Period – Analysis date of first dose intake + 1) / 365.25

With 'Analysis date of first dose intake' defined in Section 6.5.4

• Time to chronic dialysis or renal transplant or occurrence for a subject who died

Occurrence of chronic dialysis or renal transplant (whichever occurring first) during the Safety Emergent Period (see Section 6.2) will be calculated.

Time to occurrence for a subject who died during the Safety Emergent Period (see Section 6.2) will be calculated.

For a subject, the time to chronic dialysis or renal transplant or occurrence for a subject who died will be calculated (in years) as:

(First event date – Analysis date of first dose intake + 1) / 365.25

With 'First event date' defined as 'first occurrence of chronic dialysis or renal transplant, occurrence of subject who died (whichever occurring first)' and 'Analysis date of first dose intake' defined in Section 6.5.4

For a subject without event, the time to censoring will be calculated (in years) as:

(End of Safety Emergent Period – Analysis date of first dose intake + 1) / 365.25

With 'Analysis date of first dose intake' defined in Section 6.5.4

• Time to doubling of serum creatinine

First occurrence of serum creatinine being doubled compared with baseline during the Safety Emergent Period (see Section 6.2) will be calculated:

(First event date – Analysis date of first dose intake + 1) / 365.25

For a subject without event, the time to censoring will be calculated (in years) as:

(End of Safety Emergent Period – Analysis date of first dose intake + 1) / 365.25

With 'Analysis date of first dose intake' defined in Section 6.5.4

• Time to doubling of serum creatinine or chronic dialysis or renal transplant:

First occurrence of serum creatinine being doubled compared with baseline during the Safety Emergent Period (see Section 6.2) will be calculated. In addition, first occurrence of chronic dialysis or renal transplant during the Safety Emergent Period will be derived.

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The endpoint is defined as time to doubling serum creatinine or chronic dialysis or renal transplant what ever comes first:

(First event date – Analysis date of first dose intake + 1) / 365.25

For a subject without event, the time to censoring will be calculated (in years) as:

(End of Safety Emergent Period – Analysis date of first dose intake + 1) / 365.25

With 'Analysis date of first dose intake' defined in Section 6.5.4

• Time to chronic dialysis or renal transplant:

Occurrence of chronic dialysis or renal transplant (whichever occurring first) during the Safety Emergent Period (see Section 6.2) will be calculated and time to event in years will be defined as:

(First event date – Analysis date of first dose intake) /365.25

With 'First event date' defined as 'Date of dialysis or Date of renal transplant (whichever occurring first) and 'Analysis date of first dose intake' defined in Section 6.5.4

For a subject without dialysis or transplant, the time to censoring will be calculated as:

(Date of End of Safety Emergent Period – Analysis date of first dose intake + 1) / 365.25

With Date of End of Safety Emergent Period defined in Section 7.11.5

- Occurrence of End Stage Renal Disease is taken directly from the eCRF with the following categories: f the following:
 - Underwent >30 days of dialysis therapy
 - Received kidney transplant
 - Planned kidney transplant
 - Physician recommended renal replacement therapy and subject refused therapy
 - Began dialysis and died < 30 days later
- ESRD-free survival is defined as time form first dose alive and not progressed to ESRD. The time to event will be derived where event is death or ESRD whatever is first.

The time to event will be derived (in years) as:

(Date of event – Analysis date of first dose intake + 1) / 365.25

where 'date of event' is defined as date of occurrence of End Stage Renal Disease (recorded End Stage Renal Disease as AE) or date of death, whichever comes first, during the Safety Emergent Period.

For a subject wthout event, the time to censoring will be calculated (in years) as:

(End of Safety Emergent Period – Analysis date of first dose intake + 1) / 365.25

Proportion and Time to at least a 40% eGFR decrease from baseline, based on all eGFR values before start of acute or chronic dialysis

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Time to at least 40% decrease in eGFR from baseline, chronic dialysis or renal transplant:

First occurrence of at least 40% decrease in eGFR from baseline during the Safety Emergent Period (see Section 6.2) will be calculated.

Occurrence of chronic dialysis or renal transplant (whichever occurring first) during the Safety Emergent Period (see Section 6.2) will be calculated.

For a subject, the time to at least 40% decrease in eGFR from baseline, chronic dialysis or renal transplant will be calculated (in years) as:

(First event date – Analysis date of first dose intake + 1) / 365.25

With 'First event date' defined as 'First occurrence of 40% decrease in eGFR from baseline, first occurrence of chronic dialysis or renal transplant (whichever occurring first) and 'Analysis date of first dose intake' defined in Section 6.5.4

For a subject without event, the time to censoring will be calculated (in years) as:

(End of Safety Emergent Period – Analysis date of first dose intake + 1) / 365.25

With 'Analysis date of first dose intake' defined in Section 6.5.4

• Time to at least 40% decrease in eGFR from baseline

First occurrence of at least 40% decrease in eGFR from baseline during the Safety Emergent Period (see Section 6.2) will be calculated.

For a subject, the time to at least 40% decrease in eGFR from baseline will be calculated (in years) as:

(First event date – Analysis date of first dose intake + 1) / 365.25

With 'First event date' defined as 'First occurrence of 40% decrease in eGFR from baseline, and 'Analysis date of first dose intake' defined in Section 6.5.4

For a subject without event, the time to censoring will be calculated (in years) as:

(min[End of Safety Emergent Period, first occurrenct of chronic dialysis date] – Analysis date of first dose intake + 1) / 365.25

With 'Analysis date of first dose intake' defined in Section 6.5.4

6.1.4 Other exploratory variables: hs-CRP (High Sensitivity C-Reactive Protein) and sTFR (Soluble Transferrin Receptor)

The variables hs-CRP and sTFR will be collected from the central laboratory on the following visits: Day 1, weeks 4, 12, 20, 36, 52, EOT and EOS. Absolute values and changes from baseline to each study visit will be calculated. Baseline assessment is the assessment from Day 1 visit. If Day 1 assessment is missing, change from baseline will not be reported. Analysis windows are defined in Table 31, Section 7.11.4.

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6.2 Safety Variables

Safety will be assessed by evaluation of the following variables:

- Treatment-emergent adverse events (TEAEs; frequency, severity, seriousness, and relationship to study drug),
- Vital signs (systolic and diastolic blood pressure, pulse, respiratory rate and weight),
- Clinical laboratory variables (hematology, biochemistry including liver enzymes and total Bilirubin, and urinalysis),
- Physical examination,
- 12-lead electrocardiogram (ECG).
- Vascular Access Thrombosis

The **Safety Emergent Period** will be defined as the evaluation period from the Analysis date of first drug intake up to 28 days after the Analysis Last Dose date (defined in Section 6.5.4). Refer to Section 7.11.5 for more details on the derivation of the date of End of the Safety Emergent Period. This period will also be used to identify the minimum or maximum values collected on-treatment, defined as values collected from Day 2 up to the end of the Safety Emergent Period.

6.2.1 Adverse Events

6.2.1.1 Treatment emergent adverse event (TEAE)

TEAE is defined as an adverse event observed after starting administration of the test drug/comparative drug. If the adverse event occurs on Day 1 and the onset check box is marked "Onset after first dose of study drug" or the onset check box is left blank, then the adverse event will be considered treatment emergent. If the adverse event occurs on Day 1 and the onset check box is marked "Onset before first dose of study drug", then the adverse event will not be considered treatment emergent. If a subject experiences an event both during the pre-investigational period and during the investigational period, the event will be considered as TEAE only if it has worsened in severity (i.e., it is reported with a new start date). Only adverse events starting during the Safety Emergent Period will be counted as TEAE.

A drug-related TEAE is defined as any TEAE with at least possible relationship to study treatment as assessed by the investigator or with missing assessment of the causal relationship.

Severity of AEs will be graded according to National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0.

For AE onset date imputation rules, refer to Section 7.11.2

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0.

6.2.1.2 Standardized MedDRA Queries

No standardized MedDRA Queries (SMQs) will be performed.

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6.2.1.3 Time to occurrence of a TEAE (by type of AE group)

TEAEs are also classified into a number of groups depending on the following factors:

- Serious TEAEs
- Death during the Safety Emergent Period
- Any deaths (during the 24-month period)
- Related Serious TEAEs
- TEAEs Leading to permanent Discontinuation of the study drug
- TEAEs NCI CTC Grade 3 or Higher
- MedDRA System Organ Class (SOC)

The time to occurrence for a subject with a TEAE for a given type (except any deaths) will be calculated (in years) as:

(First TEAE date of the given type during the Safety Emergent Period – Analysis date of first dose intake + 1) / 365.25

With 'Analysis date of first dose intake' defined in Section 6.5.4 All adverse events collected during the Safety Emergent Period will be counted as TEAE, irrespective of use of rescue therapy.

Subjects who have not experienced a TEAE for that given type will be censored; the subject will be censored and the time to censoring for these subjects will be calculated (in years) as:

(Date of End of Safety Emergent Period – Analysis date of first dose intake +1) / 365.25

With date of end of Safety Emergent Period defined in Section 7.11.5

For any deaths during the 24-month period (including those occurring during the Post-Study Follow Up Period), time to occurrence for a subject who died during study / post study follow up) will be calculated (in years) as:

[End date for corresponding Fatal AE – Analysis date of first dose intake + 1] / 365.25

With 'End date for corresponding Fatal AE' which cover both study and post-study FU occurring up to Day 760 (i.e., month 24 + one month follow up + 3 days window as per protocol).

Subjects who have not died; the subject will be censored and the time to censoring for these subjects will be calculated (in years) as:

Minimum between [Day 760 and Max (Date of last known date when subject alive (End of Post-study FU), Date of lastcontact (Post study FU visit/call), Date of last Study evaluation (EOS form)) – Analysis date of first dose intake +1) / 365.25

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Additional analyses censoring data post dialysis:

Time to occurrence with censoring all data at the initiation of permanent dialysis will be calculated as above where events occurring after initiation of dialysis will not be considered.

Subjects who initiated dialysis and who have not experienced an event prior to the dialysis will be censored and the time to censoring for these subjects will be calculated (in years) as:

Subjects who have not experienced an event and did not initiate dialysis during the Safety Emergent Period, the time to censoring will be calculated (in years) as

(Date of End of Safety Emergent Period – Analysis date of first dose intake +1) / 365.25.

6.2.1.4 AE within 7 days

Additional analyses restricted to AEs that observed after starting administration of the test drug/comparative drug and up to Analysis Date of Last Dose + 7 days wil be defined. If the AE occurs on Day 1 and the onset check box is marked "Onset before first dose of study drug", then the adverse event will not be considered.

Time to occurrence of event will be calculated (in years) as:

(First event date of the given type occurring from Day 1 (post dose) up to Analysis date of minimum of (Last Dose + 7 days, end of safety period)) – Analysis date of first dose intake + 1) / 365.25

With 'Analysis date of first dose intake' defined in Section 6.5.4 and Analysis Date of Last Dose defined in Section 6.5.3

Subjects who have not experienced an AE for that given type will be censored; the subject will be censored and the time to censoring for these subjects will be calculated (in years) as:

Minimum [Analysis Date of Last Dose + 7 days, *Max* (EOS, Date of Death)] – Analysis date of first dose intake +1) / 365.25

6.2.1.5 Definition of incidence rate

The incidence rate (per 100 subject years at risk) will be calculated as follows:

$$\frac{\text{Number of subjects with event}}{\text{Total cumulative time at risk (years)}} \times 100$$

Where Total cumulative time at risk is the sum of individual time at risk defined as either time to occurrence of the event or time to censoring for subjects with no event. Time to occurrence of the event and time to censoring are defined in Section 6.2.1.3

Number of subjects at risk is defined as the number of subjects with (censored or non-censored) times to the event of interest greater or equal to t.

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6.2.1.6 Definitions of event rate

The event rate (per 100 patient year) during the Safety Emergent Period will be calculated as either:

$$\frac{\text{Number of events}}{\text{Patient Exposure Years}} \times 100$$

Or

Where Patient Exposure Years is defined as [Sum of individual exposure in days (Analysis date of last dose – Analysis date of first dose + 1)] / [(Duration of Safety Emergent Period in days / 365.25)].

The definition used will be indicated in the description of the corresponding analysis in Section 7

6.2.2 Vital Signs

The following endpoints will be assessed:

- Systolic blood pressure (SBP)
- Diastolic blood pressure (DBP)
- Pulse

In addition, the following assessments will be done:

- Respiratory rate
- Weight

Single measurements for blood pressure (BP) will be taken at three visits during the screening period. Measurements will be taken in triplicate with 2-minute intervals for all other visits. An average will be calculated from the three readings, the average in the eCRF system will not be used.

In case of missing values within a visit, the available readings will be used.

The position and date for the assessment will also be recorded. Change from baseline will be calculated as the measurement taken at the specific visit minus the measurement at baseline visit.

For all vital parameters, the minimum and the maximum post-baseline value during the Safety Emergent Period will be defined. For this calculation, only values from day 2 up to the date of End of the Safety Emergent Period (see Section 7.11.5).

Baseline assessment is the assessment from day 1 visit. If day 1 assessment is missing, screening period assessment will be used in the analysis. For missing visits, the last observation will be carried forward

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From the assessments collected in the 'Vital Signs - HD/HDF Subjects Only' form, only the pre-dialysis ones will be used for the classification of analysis visit (see Table 31 Section 7.11.4) and the definition of potentially clinical vital signs criteria.

Vital signs values are potentially clinically significant (PCS) if they meet both the observed value criteria and the change from baseline criteria listed in Table 6 (10 combined criteria).

Table 6 Potentially Clinically Significant (PCS) Vital signs Criteria

Vital Sign Parameter	Flag	Crit	eria
		Observed Values	Change from Baseline
Respiratory Rate	High	≥ 20	Increase of ≥ 5
(breaths per min)	Low	≤ 10	Decrease of ≥ 5
Systolic Blood Pressure	High	≥ 170	Increase of ≥ 20
(mmHg)	Low	≤ 90	Decrease of ≥ 20
Diastolic Blood Pressure	High	≥ 110	Increase of ≥ 15
(mmHg)	Low	≤ 45	Decrease of ≥ 15
Pulse	High	≥ 120	Increase of ≥ 20
(beats per min)	Low	≤ 50	Decrease of ≥ 20
Weight (kg)	High	-	Increase of ≥ 10%
	Low	-	Decrease of ≥ 10%

Potentially Clinically Significant Vital Signs Criteria will be calculated at each study visit and on-treatment (at any moment during the Safety Emergent Period) using the worst value among all available measurements.

Time to occurrence of PCS Vital signs:

For each potentially clinically significant vital signs criteria (i.e., 10 combined criteria), the time to occurrence of a PCS at any moment during the Safety Emergent Period (see Section 6.2) will be calculated (in years) as:

(First occurrence date – Analysis date of first dose intake + 1) / 365.25

With 'First occurrence date' defined as the first date when both criteria (i.e on observed and change from baseline) are met and Analysis date of first dose intake' defined in Section 6.5.4

Subjects without abnormality will be censored and time to censoring for these subjects will be calculated (in years) as:

(Date of last vital signs assessment where the parameter analyzed is non-missing during the Safety Emergent Period – Analysis date of first dose intake +1) / 365.25

Post-dialysis Vital Signs data will be listed and PCS criteria (observed value) only will be evaluated for them and flagged in the listing. No summary tables or Time to Event will be performed for them due to insufficient data.

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6.2.3 Clinical laboratory variables

6.2.3.1 Potentially Clinically Significant (PCS) Laboratory Criteria

Laboratory test values are potentially clinically significant (PCS) if they meet either the low or high PCS criteria listed in Table 7 below.

Potentially Clinically Significant (PCS) Laboratory Criteria Table 7

Potentially Clinically Significant Laboratory Criteria			
Laboratory Parameter	Unit	Low PCS Criteria	High PCS Criteria
Alanine Aminotransferase (ALT)		no lower limit	> 3X ULN
			$> 5X ULN^{\#}$
	U/L		> 8X ULN [#]
			> 10X ULN#
			> 20X ULN [#]
Aspartate Aminotransferase		no lower limit	> 3X ULN
(AST)			$> 5X ULN^{\#}$
	U/L		> 8X ULN [#]
			$> 10 X ULN^{\#}_{\mu}$
			> 20X ULN [#]
Alkaline Phosphatase (ALP)	U/L	no lower limit	> 1.5 X ULN#
			> 3 X ULN
ALT or AST	U/L for ALT or AST	no lower limit	ALT or AST > 8X ULN
Total Bilirubin	μmol/L	no lower limit	> 1.5 X ULN
	•		> 2 X ULN [#]
Moderate Liver Abnormality**	U/L for ALT and AST,	no lower limit	ALT and/or AST > 3X
	μmol/L for Total		ULN or Total Bilirubin >
C T' A1 1' Make	Bilirubin	1 1' '	2X ULN
Severe Liver Abnormality**	U/L for ALT and AST,	no lower limit	ALT and/or AST $> 3X$
	μmol/L for Total		ULN and Total Bilirubin
Gamma Glutamine Transaminase	Bilirubin U/L	no lower limit	> 2X ULN
(GGT)	U/L	no lower limit	> 3X ULN
Calcium	mmo1/L	< 0.8 X LLN	>1.2 X ULN
Creatinine	μmo1/L		>1.5 X Baseline
Potassium	mmo1/L	< 0.75 X LLN	>1.2 X ULN
Sodium	mmo1/L	< 0.9 X LNL	>1.1 X ULN
Total Protein	g/L	< 0.9 X LNL	>1.1 X ULN
Blood Urea Nitrogen (BUN)	mmo1/L		>1.5 X Baseline
Neutrophils	$10^{6}/L$	≤1000	
Platelet Count	10 ⁹ /L	≤100	≥700
White Blood Cell Count	$10^9/L$	≤2.5	≥15
Triacylglycerol/Lipase	U/L	no lower limit	> 3X ULN or > 2 X
			Baseline
LLN: Lower limit of normal, value provided by the laboratory			
ULN: Upper limit of normal, value provided by the laboratory			

Potentially Clinically Significant Laboratory Criteria will be calculated at each study visitand on-treatment (see Section 6.2) using the worst value among all available measurements,

^{*}Hemoglobin in SI unit (for conventional unit g/dL, divide by 10)

^{**} a subject's ALT and Total Bilirubin laboratory draw date or AST and Total Bilirubin laboratory draw date must occur on the same blood sample in order to be counted.

[#] Additional criteria required for summary of Liver Function Tests only (see Section 7.5.2.1)

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except for Moderate and Severe Liver Abnormalities which will be calculated on-treatment only.

Time to occurrence of an abnormality (for selected criteria)

Time to occurrence of an abnormality, will be derived only for the following PCS criteria:

- Hemoglobin <6 g/dL
- Hemoglobin >14 g/dL
- Alanine Aminotransferase (ALT) > 3X ULN
- Aspartate Aminotransferase (AST) > 3X ULN
- Total Bilirubin > 1.5 X ULN

For each potentially clinically significant laboratory criteria, the time to occurrence of an abnormality for a subject with an abnormality at any moment during the Safety Emergent Period (see Section 6.2) will be calculated (in years) as defined in Section 6.2.2

Time to censoring will be defined (in years) as:

(Date of last laboratory assessment where parameter analyzed is non-missing during the Safety Emergent Period – Analysis date of first dose intake +1) / 365.25

6.2.3.2 Laboratory assessments

For all laboratory parameters, the minimum and the maximum values on treatment (see Section 6.2) will be defined.

In addition, each laboratory result will be classified as low (L), normal (N), or high (H) at each visit according to the laboratory supplied reference ranges.

Change from baseline will be calculated as the measurement taken at the specific visit minus the measurement at baseline visit.

Baseline assessment is the assessment from the day 1 visit, except for Hb (see Section 6.1.1).

If Day 1 is missing, the screening or unscheduled assessment that is closest prior to Day 1 will be used.

Screening is defined as the screening or unscheduled assessment that is closest to Day 1.

For the lipid panel and glucose parameter, two baseline values will be defined based on fasting status: regardless of fasting and fasted.

6.2.4 Physical Examination

A comprehensive physical examination will be conducted during the screening period and at the EOT visit and recorded in the source documents. This examination will include general appearance and the following body regions and systems: head, eyes, ears, neck and throat (HEENT), lungs, heart, chest and back, abdomen, genitourinary, extremities, skin and any other, if deemed necessary.

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A targeted examination (e.g., respiratory and cardiovascular) will be conducted and recorded in the source documents.

Only the date of the physical examination will be recorded in the eCRF. There will be no table or listing for the physical examination. Any clinically relevant adverse change will be recorded as an AE in the eCRF.

6.2.5 12-lead Electrocardiogram (ECG)

The 12-lead ECG measurements will be performed on all subjects at specific times. A single ECG measurement will be taken with the subject in the supine position, after the subject has been lying quietly for 5 minutes. Clinically significant abnormalities will be reported as an AE.

The visit, ECG date, Pulse, RR Interval, PR interval, QRS Interval, QT Interval, overall interpretation and relevant comments will be recorded in the eCRF.

Baseline assessment is the assessment from day 1 visit. If day 1 assessment is missing, screening period assessment will be used in the analysis.

QTc interval will be calculated using both

- Bazett (QTcB = QT/(RR Interval) $^{1/2}$) and
- Fridericia (QTcF = QT/(RR Interval) $^{1/3}$) corrections,

where QT is in msec and RR Interval in seconds; and if RR Interval is not available, it will be replaced with 60/HR.

For all ECG parameters, the maximum post-baseline value on treatment will be defined (see Section 6.2).

ECG values are potentially clinically significant (PCS) if they meet or exceed the upper limit values listed in Table 8 below.

Table 8 ECG Parameters classification

ECG Parameter	Classsification
QTc interval (msec) > 450 msec, > 480 msec, > 500 msec;	
QTc interval change (msec)	> 30 msec and > 60 msec
	(increase from baseline)
QRS (msec)	≥ 150 msec
PR (msec)	≥ 250 msec

Time to occurrence of PCS ECG:

For the two QTc criteria (QTc > 500 msec; change from baseline in QTc > 60 msec), the time to occurrence (in years) for a subject with occurrence of the PCS at any moment during Safety Emergent Period (defined in Section $\boxed{6.2}$) will be calculated (in years) as defined in Section $\boxed{6.2.2}$

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Time to censoring will be defined as:

(Date of last ECG assessment where parameter analyzed is non-missing during the Safety Emergent Period – Analysis date of first dose intake +1) / 365.25

6.2.6 Vascular Access Thrombosis (VAT)

For each AE listed as VAT, additional information regarding the event will be recorded.

6.3 Pharmacokinetic Variables

All details of the population PK analysis will be described in a separate analysis plan.

6.4 Pharmacodynamic Variables

Not applicable.

6.5 Other Variables

6.5.1 Eligibility criteria

Eligibility at screening will be recorded as a yes/no variable for each criterion. The date of the informed consent for the subjects will also be documented.

6.5.2 Demographic and Baseline Characteristic Variables

Demographic characteristics will be recorded at screening (sex, the day, month and year of birth, age, race, height and weight).

Collection of date of birth depends on local regulations. Day of birth will be recorded in the eCRF as the first of the month when the day is not allowed to be collected. In cases where only year of birth is allowed to be collected, day and month will be recorded in the eCRF as the first of January. Age will be recalculated in SDTM and ADAM datasets.

If D_B is the Date of Birth and D_{First} is the Date of First Dose intake, Age is Age= $(D_{First}-D_B+1)/365.25$. If the Date of First Dose intake is not available, Date of Informed Consent will be used.

Based on recalculated age, three categories will be defined:

- < 65 years
- 65 74 years,
- \geq 75 years

Each subject's body mass index (BMI) will be calculated as:

BMI
$$(Kg/m^2)$$
 = Weight $(Kg)/[Height (m)]^2$,

in which the height will be converted from cm. into m. by dividing by 100.

Tobacco history and use will be recorded at screening.

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The average maximum quantity of tobacco per week will be calculated using the average maximum quantity and frequency filled in the CRF. If the frequency is "Day", the average maximum quantity of tobacco per week will be determined as follows:

average maximum quantity per day x 7

If the frequency is "/Month", the average maximum quantity of tobacco per week will be determined as follows:

average maximum quantity per month / 4.3482

Screening Hb will be defined as the mean of the three latest central laboratory Hb values prior to the day of randomization.

Baseline Hb is defined in Section 6.1.1

Based on the mean screening Hb value, two categories will be defined:

- $\leq 8.0 \text{ g/dL}$
- > 8.0 g/dL

History of cardiovascular, cerebrovascular or thromboembolic diseases at baseline will be determined by performing a medical review of preferred terms recorded on any of the medical history forms. History will be categorized as:

- Yes
- No

Countries and Regions

Subjects will be enrolled from the following countries:

Region A (Western Europe)

- Spain
- UK
- Italy
- Belgium

Region B (Rest of the World)

- Bulgaria
- Hungary
- Russia
- Romania
- Poland
- Turkey
- South Africa
- Serbia
- Ukraine
- Georgia

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- Estonia
- Greece
- Panama
- Peru
- Guatemala
- Columbia
- Dominican Republic
- Belarus

Region B includes additional countries which were not part of the initial list of countries from Central and Eastern Europe as per IRT due to extended recruitment in Central and South Americas as well as Africa.

Randomization will be stratified by region using two categories:

- Region A: Western Europe
- Region B: Rest of the World

A limited amount of subjects is expected to be recruited out of Europe and will be randomized under the Central and Eastern Europe level of the Interactive Response Technology .

Time to Treatment Discontinuation

Time to Treatment Discontinuation in years is defined as:

Time to Treatment Discontinuation (years) = ('Date of Treatment Discontinuation - ('Analysis date of first dose intake +1)/365.25

In case a subject completed the treatment period, time to censoring will be calculated as:

(Analysis date of last dose – Analysis date of first dose intake + 1) / 365.25

With Analysis data of last dose defined in Section 6.5.4

Time in years from Diagnosis of Anemia

Time from diagnosis of anemia in years is defined as:

Time from Diagnosis of Anemia (years) = ('Analysis date of first dose intake '-'Date of Diagnosis')/365.25

In case of partial dates, imputation rules apply and are detailed in Section 7.11.2

Time in years from Diagnosis of CKD

Time from diagnosis of CKD in years is defined as:

Time from Diagnosis of CKD (years) = ('Analysis date of First Dose intake '-'Date of Diagnosis of CKD')/365.25

In case of partial dates, imputation rules apply and are detailed in Section 7.11.2

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Time from Diagnosis of Targeted Medical History

Onset date and the start date of analysis for the study drug are collected and the time from diagnosis of targeted medical history in years is defined as

Time from Diagnosis of Targeted Medical History (years) = ('Analysis date of first dose intake' - 'Onset Date')/365.25

In case of partial dates, imputation rules apply and are detailed in Section 7.11.2

This will be calculated for each patient who was diagnosed with the targeted medical history: hypertension, diabetes mellitus type 1, type2 and combined, dyslipidemia and vascular access.

eGFR

eGFR will be provided by the central laboratory only for the selected visits as described in the schedule of assessments. It will be calculated by the central lab using the following 4-variable Modification of Diet in Renal Disease (MDRD) equation:

eGFR (in mL/min per 1.73m^2) = 175 x (SCr in mg/dL)^{-1.154} x (Age in years)^{-0.203} x (0.742 if female) x (1.21 if African American)

where SCr = serum creatinine concentration.

Since SCr will be collected for all the selected visits above plus additional ones, eGFR will be derived using the same formula and the derived eGFR will be used for the analysis. Checks will be performed by programming in order to ensure that derived eGFR values will match with eGFR provided by ICON for the selected visits.

Screening eGFR will be classified in the following categories : $< 30 \text{ mL/min}/1.73 \text{ m}^2 \text{ versus}$ $\geq 30 \text{ mL/min}/1.73\text{m}^2, \text{ and } < 10,10 < 15 \text{ 15} < 30, 30 < 45, 45 < 60, \text{ and } >= 60 \text{ mL/min}/1.73\text{m}^2$

Iron Repletion at Screening

Subjects will be classified in one of the following four groups according to the TSAT and ferritin levels collected at Screening (prior to first drug intake):

- ferritin < 30 ng/mL or TSAT < 5%
- $30 \le \text{ferritin} < 100 \text{ ng/mL} \text{ and } 5\% \le \text{TSAT} < 20\%$
- 30 < ferritin < 100 ng/mL and TSAT > 20%
- ferritin > 100 ng/mL and 5% < TSAT < 20%
- ferritin > 100 ng/mL and TSAT > 20%

Regarding Iron Repletion at screening, both TSAT and Ferritin should be coming from the same blood sample in cases that we have more than one record.

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Iron Repletion at Baseline

Subjects will be classified in one of the following four groups according to the TSAT and ferritin levels collected on Day 1:

- ferritin < 30 ng/mL or TSAT < 5%
- 30 < ferritin < 100 ng/mL and 5% < TSAT < 20%
- $30 \le \text{ferritin} < 100 \text{ ng/mL} \text{ and TSAT} \ge 20\%$
- ferritin $\geq 100 \text{ ng/mL}$ and $5\% \leq TSAT \leq 20\%$
- ferritin > 100 ng/mL and TSAT > 20%

Regarding Iron Repletion at baseline, both TSAT and Ferritin should be coming from the same blood sample in cases that we have more than one record on Day 1. If no Day 1 assessment is available, Iron Repletion at Screening will be used.

Use of ESAs during the last year prior to start of study treatment

Subjects will be classified as either having used or not ESAs during the last year. Previous use of ESAs is collected in the Treatment History for Anemia Form.

6.5.3 Previous and concomitant medication

Previous medication is defined as a medication with at least one dose taken before the date of first dose of study drug.

Concomitant medication is defined as a medication with at least one dose taken between the date of first dose (inclusive) and the date of the End of the Safety Emergent Period.

Previous and concomitant drug use will be recorded, including non-prescription medication, complementary and alternative medications. Handling of missing date information for prior or concomitant medications is given in Section 7.11.2

If the medication start date and end date are both missing, the medication will be counted as both previous and concomitant.

If the medication start date is missing and the end date is prior the date of first drug administration, the medication will be counted as previous medication.

If the medication start date is missing and the end date is after the date of first drug administration, the medication will be counted as concomitant medication.

6.5.4 Variables related to study drugs

Randomization/Treatment Arms

<u>Table 9</u> below presents the groups to which subjects are randomized under the initial protocol version 1.0.

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Table 9 Randomization arms under Protocol version 1.0

Randomization	Correction Period	Maintenance period	
Arm Code			Randomization Arm
(OARMCD)			(OARM)
1A	TIW	QW	Roxadustat TIW/QW
1P	TIW	QW	Placebo TIW/QW
2A	TIW	BIW	Roxadustat TIW/BIW
2P	TIW	BIW	Placebo TIW/BIW
3A	TIW	TIW	Roxadustat TIW/TIW
3P	TIW	TIW	Placebo TIW/TIW

Table 10 below presents the groups to which subjects are randomized under protocol version 2.0 and later.

Table 10 Treatment arms under protocol version 2.0

Randomization Arm Code (ARMCD)	Randomization Arm (ARM)
A	Roxadustat
В	Placebo

For the statistical analysis, treatments will be pooled across placebo and roxadustat under both protocol versions.

Analysis date of First Dose Intake

Date of first study drug dose intake is collected in the Day 1 visit in the Randomization eCRF. In case of a missing/partial date, the earliest available date will be used. It will be on the same day than the randomization date and before the next dose date.

Analysis Date of Last Dose

Date of Last Study Drug Dose is collected at the End of Extended Treatment visit in the End of Extended Treatment eCRF. When this date is not known, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts have been made, then the visit date of the End of Extended Treatment Visit will be used as the Analysis Date of Last Dose. If subject is lost to follow-up and none of these dates are available then the date of the last available assessment during the study will be used.

If analysis date of last dose is missing due to fact that date of last dose is a partial date with day unknown (month and year populated), then minimum between the date of death and end of month for the partial date will be used.

Duration of exposure in days (overall)

For each subject, the Length of Time on treatment will be calculated in days, using the following formula:

('Analysis Date of Last Dose' - 'Analysis Date first dose intake') + 1

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Amount of Prescribed (planned) Medication

The number of milligrams prescribed at each visit (including unscheduled visits) is captured in the *Changes in Dosing* eCRF. The investigator reported dose and frequency will be used when available. When the investigator reported dose and frequency are not available, the IRS reported dose and frequency will be used.

The prescribed daily and weekly dose at each visit (including unscheduled visits) will be calculated as follows:

Daily Prescribed dose in mg is Prescribed weekly Dose divided by 7

Prescribed weekly dose is defined as prescribed dose x 3 as the prescribed frequency is TIW for study drug for patients randomized following protocol amendment 2.0. For patients randomized prior protocol amendment 2.0, other prescribed frequencies may be entered in the eCRF and should be used for the calculation of the prescribed weekly dose.

Each visit will have an associated start and end date as follows:

- Each visit (including unscheduled) has an associated date. This is the start date.
- Each visit (including unscheduled) will have an associated end date. This date will be the date of the next consecutive visit [including unscheduled visits and EOT] minus 1 day. This is the end date.

Time periods of interest are defined below (monthly is defined as a period of 4 weeks or 28 days) as follows:

Table 11 Time periods of interest

Time Period	Analysis Start Day	Analysis End Day*
Week 4 (Month 1)	Day 1	Day 28
Week 8 (Month 2)	Day 29	Day 56
Week 12 (Month 3)	Day 57	Day 84
Week 16 (Month 4)	Day 85	Day 112
Week 20 (Month 5)	Day 113	Day 140
Etc		
Week 104 (Month 26)	Day 701	Day 728
Overall Treatment Period	Day 1	End Day of Extended Treatment Period
Day 1 - Week 24	Day 1	End Day of Month 6 (day 168)
Day 1 – Week 36	Day 1	End Day of Month 9 (day 252)
Day 1 – Week 52	Day 1	End Day of Month 12 (day 364)

^{*}or EOT whichever is first

This will allow us to calculate the amount of prescribed medication in a time period as the sum of the daily prescribed amount within the time windows defined above.

In addition, amount of prescribed medication in mg/kg will be calculated. To convert a dose given in mg into a dose in mg/kg, the body weight recorded at day 1 will be used.

^{**}Extended treatment period only applies for subjects who do not discontinue prior to week 52.

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Amount of Consumed Medication

The consumed Investigational Product Medication is captured in the *Study Drug Accountability* eCRF which includes the following kit information:

- Kit strength, kit treatment, kit dispensed, date of kit dispensed, kit strength total number of tablets dispensed
- Kit returned, returned date, total number of tablets returned

For each kit, the following will be calculated:

- Start Day of Exposure for each kit: study day kit dispensed
- End Day of Exposure for each kit: study day kit returned 1 Day
- Amount dispensed for each kit: kit strength x number of tablets dispensed
- Amount returned for each kit: kit strength x number of tablets returned
- Amount consumed for each kit: amount dispensed amount returned
- Daily consumed dose for each kit: amount consumed/(end day of exposure-start day of exposure +1)

The same methodology as described for Amount Prescribed (planned) Medication will apply to calculate amount of consumed medication for each time period by summing up the different daily consumed amount of the different kits on a given day (subjects will be dispensed more than one kit on a given visit).

In addition, amount of consumed medication in mg/kg will be calculated.

Compliance

Compliance will be calculated for the time periods defined in Amount of Prescribed (planned) Medication. Compliance in % will be calculated for each time period (not reported cumulatively) as:

Amount consumed during time period Amount prescribed during time period × 100

The following compliance categories will be defined:

- less than 50% (significant drug noncompliance)
- at least 50%, less than 75% (moderate drug noncompliance)
- at least 75%, less than 125% (acceptable compliance)
- greater or equal 125% (drug over compliance)
- unknown

Dose Changes

Dosing changes are collected in the Study Drug - Dosing Decisions eCRF.

 A dose change is the change in the number of milligrams on the dose per intake (for example from 200 mg to 250 mg).

For example a change from 200 TIW to 250 TIW is a change of 600 mg to 750 mg per week which is regarded as a change in intake dose.

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For each subject the total number of dose changes will be calculated.

7 STATISTICAL METHODOLOGY

7.1 General Considerations

- All statistical comparisons will be made using two sided tests at the α =0.05 significance level unless specifically stated otherwise. Null hypotheses for superiority testing will be of no treatment difference and corresponding alternative hypothesis will be two-sided. Null hypotheses for non-inferiority testing will be of inferiority of roxadustat treatment and will be one-sided at the α =0.025.
- All data processing, summarization, and analyses will be performed using SAS® Version 9.3 (SAS Enterprise Guide 4.3) or higher. Specifications for tables, data listings and figures (TLFs) formats can be found in the TLF Specifications for this study.
- All data will be summarized by treatment arm (roxadustat and placebo) and for the total, unless specified otherwise.
- For continuous variables that are recorded as "< X" or "> X", the value of "X" will be used in the calculation of summary statistics. The original values will be used for the listings.
- All percentages will be rounded to one decimal place and lined up by the decimal place. The percentage will be suppressed when the count is zero.
- Any p-values will be rounded to four decimal places and will be presented as '< 0.0001' if they are less than 0.0001 after rounding.
- For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation, median, minimum and maximum. Frequencies and percentages will be displayed for categorical data. Percentages by categories will be based on the number of subjects with no missing data, i.e., will add up to 100%. Number of missing values will be shown in the frequencies tables
- All data included in summary tables, inferential analyses or figures will also be listed.
- Listings will be done on all randomized subjects and all assessments (all collected data in the eCRF will be listed except the physical examination data).
- Model checking will be performed using graphical outputs provided by the SAS procedures.

For the definition of subgroups of interest please refer to Section 7.8

7.2 Study Population

For this section, unless specified otherwise, PPS refers to the analysis set which excludes from the FAS all the subjects criteria listed in Table 3 See Section 5.3 for more details.

7.2.1 Disposition of Subjects

The following subject data will be summarized and presented:

 Number and percentage of subjects with informed consent, who discontinued before randomization and randomized (overall only);

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- Number and percentage of subjects randomized in each analysis set, by treatment arm and overall;
- Number and percentage of subjects who completed and discontinued treatment in each period (primary treatment period and extended treatment period), by primary reason for treatment discontinuation and by treatment arm for All Randomized, SAF, FAS and PPS;
- Number and percentage of subjects who completed and discontinued the study, by primary reason for study discontinuation and by treatment arm for All Randomized and SAF;
- Number and percentage of subjects who completed and discontinued the post study follow-up period for All Randomized and SAF, and
- Number and percentage of subjects excluded from PPS by reason for exclusion defined in Section 5.3 by treatment arm for the FAS.

The following data will be presented graphically by treatment arm for the FAS and the SAF:

- Treatment discontinuation by reason using bar chart;
- Treatment discontinuation by time interval and reason using bar chart; and
- Time to treatment discontinuation using a Kaplan-Meier plot.

In addition, the following graphs will be done by treatment arm, for the FAS and PPS:

- Treatment discontinuation for lack of efficacy using a cumulative incidence plot;
- Treatment discontinuation for adverse event using a cumulative incidence plot.
- Treatment discontinuation for withdrawal by subject using a cumulative incidence plot.

Time intervals will be analyzed using the following categories:

- Less than 2 weeks
- At least 2 weeks, less than 4 weeks
- At least 4 daweeks, less than 12 weeks
- At least 12 weeks, less than 24 weeks
- At least 24 weeks, less than 36 weeks
- At least 36 weeks, less than 52 weeks
- At least 52 weeks, less than 78 weeks
- 78 weeks or more
- Unknown.

In addition, the randomization stratification strata from both sources (CRF and IRT) will be reported by treatment arm. Discrepancy between stratification from CRF and IRT will be summarized and the total number of patients with discrepancy overall and for each stratification factor will be provided

Subjects who screened failure will also be listed.

All data collected during the Post-Study Follow up period will be listed by visit (i.e type of contact, subject status and occurrence of overnight hospitalizations).

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7.2.2 Protocol Deviations

Protocol deviations, as defined in the study protocol (Section 8.1.6: Protocol Deviations) will be assessed for all randomized subjects. The number and percentage of subjects meeting any criteria will be summarized for each criterion and overall, by treatment arm, as well as by study site. Subjects deviating from a criterion more than once will be counted once for the corresponding criterion. Subjects who have more than one protocol deviation will be counted once in the overall summary. A data listing will be provided by site and subject.

The protocol deviation criteria will be uniquely identified in the summary table and listing. The unique identifiers will be as follows:

- PD1 Entered into the study even though they did not satisfy entry criteria,
- PD2 Developed withdrawal criteria during the study and was not withdrawn,
- PD3 Received wrong treatment or incorrect dose
 - o PD3 1- Received wrong treatment kit
 - PD3 2- Received incorrect dose
- PD4 Received excluded concomitant treatment

7.2.3 Demographic and Other Baseline Characteristics

Demographic and other baseline/screening characteristics will be summarized by descriptive statistics and frequency tabulations.

Number and percentage of subjects randomized in each country and site will be presented for the All Randomized and SAF. Descriptive statistics for age, weight, body mass index (BMI) and height at baseline will be presented. Frequency tabulations for sex and race will be presented. Descriptive statistics and frequency tabulations will also be presented for the subgroup variables presented in Section 7.8 Additionally, demographic and other baseline characteristics will be presented for the following variables:

- Baseline and Screening Hb value as continuous and categorical (≤ 8.0 g/dL versus >8.0 g/dL),
- Baseline and Screening eGFR value as continuous and categorical ($< 30 \text{ mL/min}/1.73 \text{ m}^2 \text{ versus} \ge 30 \text{ mL/min}/1.73\text{m}^2$, and < 10, 10 < 15, 15 < 30, 30 < 45, 45 < 60, and $> = 60 \text{ mL/min}/1.73\text{m}^2$
- History of previous treatment with ESA: Yes vs. No.

Demographic and baseline characteristics summaries above will be done for the All Randomized, SAF, FAS and PPS. This table will be repeated for subjects randomized after Amendment 2.0 is implemented.

Selected demographics collected at screening will be done on Screen Failure subjects.

All Medical History will be analyzed using the SAF, as described below:

Medical History other than anemia, CKD, cardiovascular disease and targeted medical history are coded in MedDRA, they will be summarized by System Organ Class and Preferred Term.

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Anemia history, CKD history, targeted medical history, cardiovascular history, tobacco history and family history of cardiovascular disease will be summarized.

The number and proportion of subjects with each typical symptom for CKD will be described, as well as the number and proportion of subjects with each typical symptom for anemia.

Demographic and baseline data will also be listed.

7.2.4 Previous and Concomitant Medications

Previous and concomitant medications are coded with WHO-DD, and will be summarized by therapeutic subgroup (ATC 2nd level), chemical subgroup (ATC 4th level) and preferred WHO name for the SAF.

Subjects taking the same medication multiple times will be counted once per medication.

Treatment history for anemia will be summarized separately.

Missing dates' imputation rules are detailed in Section 7.11.2

7.3 Study Drugs

Roxadustat (=Investigational Product Medicine) is for oral administration and supplied as red coated oval tablets of 20, 50 and 100 mg. Roxadustat and placebo tablets are identical in size, shape and color to preserve the blinding method.

7.3.1 Exposure

The following information on drug exposure will be presented by treatment arm and overall, for the SAF.

Exposure related variables are defined in Section 6.5.4

Descriptive statistics will be produced for:

- The amount of drug (roxadustat and placebo) the subject was exposed to during the treatment period (in mg and in mg/kg), by month, during the first 24, 36, 52 weeks and overall;
- Number and percentage of subjects with dose increases, decreases or interruptions during the treatment period.

Duration of exposure will be summarized in two ways:

- Descriptive statistics will be presented overall, during the first 24 weeks, 36 weeks and 52 weeks;
- Exposure time will be categorized overall, and by treatment period, according to the following categories (and frequency tabulations):
 - Less than 2 weeks
 - O At least 2 weeks, less than 4 weeks
 - o At least 4 weeks, less than 12 weeks
 - O At least 12 weeks, less than 24 weeks

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- o At least 24 weeks, less than 36 weeks
- o At least 36 weeks, less than 52 weeks
- o At least 52 weeks, less than 78 weeks
- o 78 weeks or more
- Unknown.

Box-plots of monthly dose and monthly dose/kg by month will be produced by treatment arm (roxadustat and placebo).

Study drug medication will also be listed showing for each subject and each visit the dispensed kit numbers and the actual medication in each kit. For instance, if a subject randomized to placebo, at one visit was mistakenly dispensed a kit containing roxadustat then the listing will show that roxadustat was given to the subject on the intended visit.

7.3.2 Treatment Compliance

Overall compliance with the dosing schedule will be examined for subjects in the SAF whose total study drug count and first and last days of treatment are known.

Percent overall compliance will be summarized in two ways, by month, by treatment period, during the first 24 weeks, 36 weeks, 52 weeks and overall:

- Descriptive statistics will be presented,
- Percent compliance categories will be categorized according to the categories defined in Section 6.5.4

Counts and percentages of subjects in each of these categories will be summarized.

Results will be displayed by treatment arm and overall.

7.4 Analysis of Efficacy

For all continuous efficacy variables, in addition to inferential analyses, descriptive statistics will be produced for the actual values and for the changes from baseline (BL) by visit.

Similarly, for all categorical efficacy variables, frequencies and proportions will be produced by analysis visit.

Quantitative endpoints with repeated measures over time will be analyzed using MMRM and ANCOVA with Multiple Imputations (MI) as the preferred methods for imputation of missing data, as per FDA recommendation at the time of SPA assessment of FGCL-4592-060.

For this section, PPS refers to the analysis set which excludes from the FAS all the subjects criteria listed in Table 3 See Section 5.3 and and Classification specifications for more details.

Analysis visits windows are detailed in Section 7.11.4

Missing data imputation rules are detailed in Section 7.11.1

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7.4.1 Analysis of Primary Endpoint(s)

There are two separate regionally based primary efficacy endpoints in this study depending upon whether the data are being filed to support submission to the EU EMA or to ex-EU health authorities, such as the US FDA.

7.4.1.1 EU (EMA) Primary Endpoint

7.4.1.1.1 Primary Analysis of the EU (EMA) Primary Endpoint

The EU (EMA) primary efficacy endpoint will be analyzed using the FAS. See Section 7.11.1 for imputation rules, in case of missing values in the evaluation period or in case of rescue therapy prior to Hb response.

The proportion of responders in the primary efficacy variable will be compared using a Cochran–Mantel–Haenszel (CMH) test adjusting for the region, history of CV, baseline Hb and baseline eGFR, comparing roxadustat to placebo.

The EU (EMA) primary hypothesis to be tested for the primary efficacy analysis is:

- H_0 : Hb responder rate in the roxadustat group = Hb responder rate in Placebo group versus
- H_1 : Hb responder rate in the roxadustat group \neq Hb responder rate in Placebo

The CMH adjusted odds ratio (roxadustat versus placebo) and its 95% confidence interval will be provided. Superiority of roxadustat versus placebo will be declared if the lower bound of the two-sided 95% confidence interval of the CMH odds ratio is higher than 1.

The SAS procedure will be similar to the following:

```
proc freq;
tables covariates*Treatment*Response / cmh;
run;
```

The covariates will be:

- Region [West Europe, Rest of the World])
- Baseline Hb values ($\leq 8 \text{ g/dL vs.} > 8 \text{ g/dL}$)
- History of cardiovascular, cerebrovascular or thromboembolic diseases (Yes vs. No)
- Baseline eGFR (<30 mL/min/1.73 m² vs. ≥30 mL/min/1.73 m²)

The analysis will use the collected eCRF data to derive these covariates. Note that the choice was made to use Baseline Hb and eGFR as covariates rather than Screening Hb and eGFR which were stratification factors since Baseline values are the latest pre-dose assessements (and no difference between Screening and Baseline is expected).

In addition, a 95% confidence interval for the proportion of each roxadustat and Placebo based on the exact method of Clopper-Pearson will be calculated and presented.

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The SAS procedure will be similar to the following:

```
proc freq;
tables Treatment / binomial(exact) alpha=0.05;
run:
```

Model checking

The assumption that the odds ratios are homogeneous across strata will be tested using the Breslow-Day test for stratified 2x2 tables. The model will be checked using covariates above defined by raw data.

In addition, this test will be repeated replacing the covariates by country. For this analysis, countries with less than 20 subjects in the FAS will be pooled in a grouped level per region.

This model checking information will be provided as part of the raw SAS outputs.

7.4.1.1.2 Secondary Analyses (sensitivity) of the EU (EMA) Primary Endpoint

Table 12 summarizes all sensitivity analyses to be performed with the EU (EMA) primary endpoint.

Table 12 Primary and sensitivity analyses for the EU (EMA) primary endpoint

Code	Set	Rescue Therapy	Endpoint	Method	Covariates
Primary	FAS	Without rescue therapy	Response	СМН	Region, history of CV, Baseline Hb and Baseline eGFR
S1	All Randomized	Without rescue therapy	Response	СМН	Region, history of CV, Baseline Hb and Baseline eGFR
S2	PPS	Without rescue therapy	Response	СМН	Region, history of CV, Baseline Hb and Baseline eGFR
S3	FAS	Regardless rescue therapy	Response	СМН	Region, history of CV, Baseline Hb and Baseline eGFR
S4	FAS	Without rescue therapy	Response	Logistic	Region, history of CV, Baseline Hb and Baseline eGFR as continuous covariates
S5	FAS*	Without rescue therapy	Response	СМН	Region, history of CV, Baseline Hb and Baseline eGFR

^{*}patients who were randomized after the implementation of protocol v2.0

For the logistic regressions, the odds ratio (roxadustat vs. placebo) and their 95% confidence intervals will be produced, if convergence achieved.

The SAS procedure will be similar to the following:

```
proc logistic;
```

```
class treatment region CV_history;
  model response = treatment region cv_history baseline_Hb
baseline_eGFR;
run;
```

For all sensitivity analyses, no hypothesis testing will be done, only confidence intervals presented and graphically represented in a forest plot.

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If a relevant baseline variable is identified for which a clinically important imbalance exists at baseline between treatment groups, additional sensitivity analysis on the primary endpoint may be performed using a logistic model adjusting for this baseline variable. This will allow the assessment of the impact of these imbalances on the treatment comparisons.

7.4.1.1.3 Additional Analyses of the EU (EMA) Primary Endpoint

The analysis of the EU (EMA) primary endpoint will be repeated by subgroup of interest. For definitions of subgroups of interest, see Section 7.8

For the EU (EMA) primary endpoint, subgroup analyses will be performed using the primary analysis in Table 12 If one of the subgroups is the same as a stratification factor, the factor will be omitted from the model.

Table 13 Additional Analyses of the EU (EMA) Primary Endpoint

Code	Set	Rescue Therapy	Endpoint*	Method	Covariates
A1	FAS	Without rescue	Response by	СМН	Region, history of CV, Baseline
		therapy	Subgroup		Hb and Baseline eGFR

^{*} Subgroup: (1) age, (2) sex, , (3) region, (4) baseline hemoglobin category, (5) history of CV, (6) Baseline eGFR category (7) Baseline CRP category and (8) Baseline Iron Repletion Status category

Subgroup analysis will be done by producing separate summaries similar to those produced for the primary analysis. In addition, forest plots will be generated per each subgroup showing subgroup factors on the y-axis and CMH adjusted odds ratios and their 95% confidence interval on the x-axis.

The potential existence of subgroup by treatment interaction will be visually inspected.

7.4.1.2 US (FDA) Primary Endpoint

7.4.1.2.1 Primary Analysis of the US (FDA) Primary Endpoint

The US (FDA) primary efficacy endpoint will be analyzed using the All Randomized Set

The change from baseline to the average Hb of weeks 28 to 52 will be computed from an analysis of covariance (ANCOVA) model with multiple imputations (MI), adjusting for covariates (covariates defined below), comparing roxadustat to placebo.

The primary hypothesis to be tested for the US (FDA) primary efficacy analysis is:

 H_0 : Hb mean change from baseline to the average level from Week 28 to Week 52 in the roxadustat group = Hb mean change from baseline in the placebo group versus:

 H_1 : Hb mean change from baseline to the average level of Week 28 to Week 52 in the roxadustat group \neq Hb mean change from baseline in the placebo group.

Difference of least square means (roxadustat minus placebo) and its $100x(1-\alpha/2)\%$ confidence interval will be estimated for the change from baseline to the average of weeks 28 to 52. Superiority of roxadustat versus placebo will be considered successful if the lower bound of the two-sided 95% confidence interval of the difference between treatment arms (roxadustat minus placebo) is higher than 0.

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The covariates will be:

- Region (West Europe, Ex-Central East Europe)
- Baseline Hb values (continuous)
- History of cardiovascular, cerebrovascular or thromboembolic diseases (Yes vs. No)
- Baseline eGFR (continous)

The analysis will not use the randomization strata as stratification errors during the randomization process may occur. The analysis will use the collected eCRF data to derive these covariates.

ANCOVA with MI model:

The MI ANCOVA model will be used to compare the roxadustat and placebo groups in a fixed sequence procedure:

The following steps will be used to conduct the primary analysis.

- 1. Generate 1000 datasets, using seed 654289, where intermittent missing hemoglobin data will be imputed for each treatment relying on non-missing data from all subjects within each treatment group using the Monte Carlo Markov Chain MCMC imputation model with treatment, baseline hemoglobin, baseline eGFR, region, history of cardiovascular, cerebrovascular or thromboembolic diseases and the available non missing hemoglobin for each scheduled Week.
 - The MCMC statement in the SAS PROC MI procedure with monotone option will be used. As a result, each dataset will only have missing ending data, or a monotone missing data pattern.
- 2. For each dataset from step 1, missing ending data (hemoglobin up through end of evaluation period) will be imputed using seed 472794. As a result, 1000 imputed complete datasets will be generated.
 - Missing data at Week 1 will be imputed using the regression imputation model with baseline stratification factor, baseline and hemoglobin from Week 1, using the SAS PROC MI procedure with the REGRESSION option in the MONOTONE statement.
 - The SAS PROC MI procedure will use data separately from each treatment subjects to impute the missing data for a specific Week (i.e. only those that need the imputation for the Week). Since subjects from the different treatment groups for that Week are excluded from the step, they will not contribute to the imputation for the Week.
 - Repeat for all other scheduled Weeks sequentially (Week 2 to the end of evaluation period). Subjects whose missing data were imputed for previous Weeks will contribute to the imputation for the current Week.

The regression imputation model includes an intercept and the slopes of the hemoglobin from previous Weeks and the stratification factors.

3. Analyze each imputed dataset using the ANCOVA using the mean of all observed or imputed Hb values within the evaluation period. The model will contain terms for baseline Hb measurement as a covariate and treatment arm and the other randomization stratification factors except screening Hb (≤8 vs >8) as fixed effects.

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4. Combine estimates from the results of each of the 1000 ANCOVA runs using SAS PROC MIANALYZE.

Report the results of the least-squares mean estimates of the change from baseline in hemoglobin during the evaluation period, the estimates of treatment effect (e.g., least-squares mean change form baseline in hemoglobin for the treatment group minus the least-squares mean change from baseline in hemoglobin for the placebo group) and the corresponding p-values and 95% CIs during the evaluation period.

All available Hb values will be used for the calculation of the average in weeks 28 to 52, as defined in analysis windows in Section 7.11.4

Hb imputation rules using MI are detailed in Section 7.11.1.

A forest plot will be generated showing strata on the y-axis and differences in mean changes from BL to the average in week 28-52 and their 95% confidence interval on the x-axis.

Model checking:

Residual plots will be produced showing the following:

- Model residuals in the y-axis and model predictions in the x-axis,
- Model residuals in the y-axis and baseline Hb in the x-axis.

Different dot styles will be used for the two treatment arms. Solid black symbols (square) will be used for roxadustat and non-solid red symbols (X) will be used for placebo.

Residual plots will be done for the ANCOVA with MI analyses (Primary, S1 and S2 in Table 14).

In addition, an empirical cumulative distribution function of the residuals will be plotted for the same ANCOVA analysis.

If a relevant baseline variable is identified for which a clinically important imbalance exists at baseline between treatment groups, additional sensitivity analyses of the primary endpoint may be performed using a logistic model adjusting for this baseline variable. This will allow us to assess the impact of these imbalances on the treatment comparisons.

Descriptive analyses

In addition to the inferential analysis, central laboratory and HemoCue hemoglobin Hb values and their associated change from baseline, will be reported descriptively by visit. For central lab Hb values, the average of weeks 28-52 will also be reported.

The following data will be presented graphically, by treatment arm:

- Hb results using mean values (+/- 95% CI) plot
- Hb change from baseline results using mean values (+/- 95% CI) plot.

A plot will be generated showing the change between the central laboratory and HemoCue hemoglobin values by visit (+/- 95% CI) during the Efficacy Emergent Period.

7.4.1.2.2 Sensitivity Analyses of the US (FDA) Primary Endpoint

Table 14 summarizes all sensitivity analyses to be performed with the US (FDA) primary endpoint.

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Table 14 Primary and sensitivity analysis for the US (FDA) primary endpoint

Code	Set	Rescue Therapy	Endpoint	Method	Covariates
Primary	All Randomized	Regardless rescue therapy	Change to the Average Hb in weeks 28-52	ANCOVA with MI	Region, History of CV, BL Hb, BL eGFR as continuous covariates
S1	FAS	Regardless rescue therapy	Change to the Average Hb in weeks 28-52	ANCOVA with MI	Region, History of CV, BL Hb, BL eGFR as continuous covariates
S2	PPS	Regardless rescue therapy	Change to the Average Hb in weeks 28-52	ANCOVA with MI	Region, History of CV, BL Hb, BL eGFR as continuous covariates
S3	All Randomized	Regardless rescue therapy	Change to the Average Hb in weeks 28-52	MMRM	Region, History of CV, visits and visits by treatment as categorical variables. BL Hb and BL eGFR as continuous covariates.
S4	All Randomized	Regardless rescue therapy	Change to the Average Hb in weeks 28-52	PMM (Last Mean Carried Forward)	Region, History of CV, BL Hb, BL eGFR as continuous covariates
S5	All Randomized	Regardless rescue therapy	Change to the Average Hb in weeks 28-52	PMM (Baseline Carried Forward, Roxadustat only)	Region, History of CV, BL Hb, BL eGFR as continuous covariates
S6	All Randomized	Regardless rescue therapy	Change to the Average Hb in weeks 28-52	PMM (Baseline Carried Forward, both groups)	Region, History of CV, BL Hb, BL eGFR as continuous covariates
S7	All Randomized	Regardless rescue therapy	Change to the Average Hb in weeks 28-52	PMM (Jump to control)	Region, History of CV, BL Hb, BL eGFR as continuous covariates
S8	All Randomized	Without rescue therapy	Change to the Average Hb in weeks 28-52	ANCOVA with MI	Region, History of CV, BL Hb, BL eGFR as continuous covariates
S9	All Randomized	Without rescue therapy	Change to the Average Hb in weeks 28-52	MMRM	Region, History of CV, visits and visits by treatment as categorical variables. BL Hb and BL eGFR as continuous covariates.

For all sensitivity analyses, no hypothesis testing will be done, only confidence intervals will be presented and graphically represented in a forest plot.

MMRM model:

An MMRM model will be run for the purpose of implicit imputation of missing data by using all the available information from the observed data up to Week 52 via the within-patient correlation structure. The analysis will be based on the estimated difference between the two

treatment arms overall mean effects throughout the evaluation period (weeks 28 to 52) based on this MMRM model.

The model will contain treatment arm, region, CV History, visits and visit by treatment as categorical variables and baseline Hb, baseline eGFR and baseline Hb by visit as continuous variables.

The unstructured covariance pattern model will be applied first. If the algorithm for unstructured covariance pattern does not converge then heterogeneous Toeplitz structure will be used instead. If this second model also does not converge, then the (homogeneous) Toeplitz structure will be tried. Finally, if none of them converge, first order autoregressive (AR (1)) as a covariance structure will be used to achieve convergence.

A similar model as the general example below will be used:

$$c_{ikjn} = intercept + \beta_n M_{baseline,ikjn} + \tau_i + \alpha_n + (\alpha \tau)_{in} + \gamma_k + \varepsilon_{ikjn}$$

where

- c_{ikjn} is each analysis visit change from baseline of subject j in treatment arm i, and stratum k at time n,
- β_n is the slope of c_{ikjn} at visit n as a function of the baseline Hb,
- $M_{baseline,ikjn}$ is the baseline measurement of subject j in treatment arm i and stratum k at time n,
- τ_i , is the mean effect of treatment arm i,
- α_n is the mean effect at time n,
- $(\alpha \tau)_{in}$ is the interaction term between treatment arm i and time n,
- γ_k is the mean effect of stratum k,
- ε_{ikin} is the residual at time n for subject j in treatment arm i and stratum k.

The SAS procedure will be similar to the following:

proc mixed;

One analysis Hb value for each visit will be used, as defined in analysis windows in Section 7.11.4 and Table 31

A forest plot will be generated showing strata on the y-axis and differences in mean changes from BL to the average in weeks 28-52 and their 95% confidence interval on the x-axis.

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In addition, MMRM least square means and 95% confidence intervals will be calculated for each visit for the difference in treatment arms. MMRM least square means and their 95% confidence intervals will be plotted versus time.

Model checking:

Residual plots will be produced showing the following:

- Model residuals in the y-axis and model predictions in the x-axis,
- Model residuals in the y-axis and baseline Hb in the x-axis.

Different dot styles will be used for the two treatment arms. Solid black symbols (square) will be used for roxadustat and non-solid red symbols (X) will be used for placebo.

Residual plots will be done for the MMRM analysis. The plot will be repeated by visit at Weeks 28, 32, 36, 40, 44, 48 and 52.

In addition, an empirical cumulative distribution function of the residuals will be plotted for the MMRM analysis.

The model will also be checked using the stratification factors used for the randomization [IRS].

Pattern Mixture Model (PMM)

PMMs provide a general and flexible framework for sensitivity analyses that allows formulating assumptions regarding missing data in a transparent and clinically interpretable manner. This is expected to address the possibility of the data being missing not at random (MNAR).

The following aspects of data missingness, may affect the estimates.

- Timing and extent of missingness
- Assumed underlying mechanism for data missingness

A. Timing and Extent of Missing Data

To assess the potential effect of data missingness on the estimate of treatment effect, subjects will be classified as full data or missing data cases. Patterns of missingness will be based on non-missing hemoglobin before the end of the evaluation period.

- Full data cases are defined as subjects with non-missing hemoglobin for all scheduled weeks of the Treatment period.
- Missing data cases are defined as subjects with a missing hemoglobin on at least one scheduled Week of the treatment period. The missing data cases are further grouped into intermittent missing and monotone missing cases.
 - Intermittent missing hemoglobin cases are defined as subjects with a missing hemoglobin for at least one scheduled week of but not on consecutive scheduled weeks up to end of the evaluation period.
 - Monotone missing hemoglobin cases are defined as subjects who have consecutive scheduled Weeks with missing hemoglobin up to the end of

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evaluation period. A subject who is a Monotone missing case could have intermittent missing hemoglobin prior to the ending Week.

Subjects will be grouped as follows:

- Full data cases
- Intermittent missing data cases
- Monotone missing data cases

Should the incidence of Monotone missing data cases and intermittent missing data cases be relatively small, then those cases will be combined so that the groups are full data cases and missing data cases. The summary of missing pattern in first 52 scheduled visits will be presented in a table/graph.

B. Assumptions on Missing Data Mechanism

In addition to the extent of data missingness, the mechanism under which missing data occur may affect the estimate of the parameter of interest.

The potential impact of missing efficacy endpoints on the estimates of treatment effects will be assessed using alternative statistical models with different underlying assumptions on the missing data mechanism (missing not at random(MNAR)) (Little and Rubin, 1987).

C. Last Mean Carried Forward

A pattern-mixture model using a last mean carried forward multiple imputation method will be used as another sensitivity analysis to explore the robustness of the ANCOVA results for the primary efficacy variables. Using this method, missing data after ending week will be imputed based on the last non-missing mean from its own treatment group.

D. PMM -Baseline Carried Forward (Roxadustat only and both groups)

The analysis is similar to "PMM – Last Mean Carried Forward". The imputation data will be generated similarly as last mean carried forward method described above but instead of using post-baseline observed data, only baseline data will be used. The similar analyses will be conduct in two scenarios.

- The baseline carried forward imputation will be performed for the roxadustat treatment group only, while for active control group, the imputation data will be generated using the last mean carried forward described above.
- The baseline carried forward imputation will be performed for the both treatment groups

E. PMM – Jump to Control

A pattern-mixture model using a Prior Visit Mean carried forward jump to control multiple imputation method (Carpenter et al, 2013) will also be used as another sensitivity analysis similar to the PMM- Prior Visit Mean carried forward except for step 3, where the joint distribution of the patient's observed and missing data are considered to be multivariate normal with mean and covariance matrix from the control (placebo) treatment arm.

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7.4.1.2.3 Additional Analyses of the US (FDA) Primary Endpoint

The analysis of the US (FDA) primary endpoint will be repeated by subgroup of interest. For definitions of subgroups of interest, see Section 7.8

For the US (FDA) primary endpoint, subgroup analyses will be performed using the primary and the third sensitivity analysis (S3 in Table 14) on the All Randomized Set. If one of the subgroups is the same as a stratification factor, the factor will be omitted from the model.

In addition, a sensitivity analysis will be performed by adding to the MMRM model all Hb values that will be collected even after the end of efficacy emergent period up to EOT (EOT + 2 weeks assessments should not be included), See analysis A3 in Table 15 below.

Table 15 Additional Analyses of the US (FDA) Primary Endpoint

Code	Set	Rescue Therapy	Endpoint*	Method	Covariates
A1	All Randomized	Regardless rescue therapy	Change to the Average Hb in weeks 28-52 by Subgroup	ANCOVA with MI	Region, History of CV, BL Hb, BL eGFR as continuous covariates
A2	All Randomized	Regardless rescue therapy	Change to the Average Hb in weeks 28-52 by Subgroup	MMRM	Region, History of CV, visits and visits by treatment as categorical variables. BL Hb and BL eGFR as continuous covariates.
A3	All Randomized	Regardless rescue therapy	Change to the Average Hb in weeks 28-52 including all Hb values	MMRM	Region, History of CV, visits and visits by treatment as categorical variables. BL Hb and BL eGFR as continuous covariates.

^{*} Subgroup: (1) age, (2) sex, (3) region, (4) baseline hemoglobin category, (5) history of CV, (6) Baseline eGFR category, (7) Baseline CRP category [only for A1] and (8) Baseline Iron Repletion Status category [only for A1]

Subgroup analyses will be done by producing separate summaries similar to those produced for the primary analysis. In addition, forest plots will be generated per each subgroup showing subgroup factors on the y-axis and change from baseline and their 95% confidence interval on the x-axis.

The potential existence of subgroup by treatment interaction will be visually inspected.

7.4.2 Analysis of Key Secondary Endpoints

The primary analysis set for the analysis of the key secondary endpoints will be the PPS for the non-inferiority tests and the FAS for the superiority tests.

All inferential analyses will evaluate the difference between the treatment arms: roxadustat versus placebo.

Once the primary hypothesis has been rejected for the EU (EMA) primary endpoint, the key secondary endpoints will be tested using a fixed sequence testing procedure, as depicted in Table 16 in order to maintain the overall two-sided type I error rate at 0.05. If the null hypothesis is rejected for a test, the claim of superiority (or non-inferiority) will be

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considered successful and the test will progress to the next comparison in sequence as follows:

Table 16 Key Secondary Endpoints fixed sequence testing procedure

Test	Analysis set	Endpoint	Comparison
1	FAS	Hb change from BL to the average Hb in weeks 28-36, without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period.	Superiority of roxadustat versus placebo
2	FAS	Change from BL in Low Density Lipoprotein (LDL) cholesterol to the average LDL cholesterol of weeks 12 to 28.	Superiority of roxadustat versus placebo
3	FAS	Use and time to first use of rescue therapy during the treatment period	Superiority of roxadustat versus placebo
4	FAS	Change from BL in SF-36 Vitality (VT) subscore to the average VT sub-score of weeks 12 to 28 for all subjects	Superiority of roxadustat versus placebo
5	FAS	Change from BL in SF-36 Physical Functioning (PF) sub-score to the average PF sub-score of weeks 12 to 28 for all subjects	Superiority of roxadustat versus placebo
6*	PPS	Change from BL in mean arterial pressure (MAP) to the average MAP value of weeks 20 to 28.	*: Non-inferiority of roxadustat versus placebo (the non-inferiority margin for the difference between groups is fixed as 2 mmHg)
7 *	PPS	Time to first occurrence of hypertension (defined as an increase from BL of \geq 20 mmHg systolic blood pressure (SBP) and SBP \geq 170 mmHg or an increase from baseline of \geq 15 mmHg diastolic blood pressure (DBP) and DBP \geq 110 mmHg	*: Non-inferiority of roxadustat versus placebo (the non-inferiority margin for the difference between groups is fixed as a hazard ratio of 1.3)
8 *	FAS	Rate of progression of CKD measured by annualized eGFR slope over time	*: Superiority of roxadustat versus placebo

^{*:} These key secondary endpoints will not be included in the hierarchical testing procedure.

No multiplicity adjustment will be done for the last three endpoints. Details of the analysis for each of these secondary endpoints are given below.

7.4.2.1 Hb change from baseline to the average Hb in weeks 28-36, without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period

Hb change from baseline to the average Hb value in weeks 28-36 will be compared by treatment arms using a MMRM model as in Section 7.4.1.2

The analysis will be similar to the analysis provided in Section 7.4.1.2 except that evaluation period will be from baseline to weeks 28-36, without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period.

The analysis will be done on the FAS.

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This superiority test will be considered successful if the lower bound of the two-sided 95% confidence interval of the difference between treatment arms (roxadustat minus placebo) is higher than 0.

An additional analysis (not part of the sequence) will be done for this endpoint on the FAS regardless the use of rescue therapy, as detailed in Table 17

Table 17 Primary and sensitivity analysis for the Hb change form BL to the average Hb in weeks 28-36

Code	Set	Rescue Therapy	Endpoint	Method	Covariates
Primary	FAS	Without rescue therapy	Change to the Average Hb in weeks 28-36	MMRM	Region, History of CV, visits and visits by treatment as categorical variables. BL Hb and BL eGFR as continuous covariates.
S1	FAS	Regardless rescue therapy	Change to the Average Hb in weeks 28-36	MMRM	Region, History of CV, visits and visits by treatment as categorical variables. BL Hb and BL eGFR as continuous covariates.

7.4.2.2 Change from BL in Low Density Lipoprotein (LDL) cholesterol to the average LDL cholesterol of weeks 12 to 28

LDL change from baseline to the average LDL value in weeks 12-28 will be compared by treatment arms using a MMRM model as in Section 7.4.1.2 (with the addition of LDL at baseline as continuous covariate). The analysis will be done on the FAS.

The analysis will be similar to the analysis provided in Section [7.4.1.2] This superiority test will be considered successful if the upper bound of the two-sided 95% confidence interval of the difference between treatment arms (roxadustat minus placebo) is below 0.

An additional analysis (not part of the sequence) will be done on the All Randomized Set, as detailed in Table 18

Table 18 Primary and sensitivity analysis for the LDL change from BL to the average LDL in weeks 12-28

Code	Set	Endpoint	Method	Covariates
Primary	FAS	Change from baseline to the Average LDL in weeks 12-28	MMRM	Region, History of CV, visits and visits by treatment as categorical variables. BL LDL, BL Hb and BL eGFR as continuous covariates.
S1	All Randomized	Change from baseline to the Average LDL in weeks 12-28	MMRM	Region, History of CV, visits and visits by treatment as categorical variables. BL LDL, BL Hb and BL eGFR as continuous covariates.

For missing LDL imputation rules for MMRM refer to Section 7.11.1

Theses analyses will be done on all values (regardless the fasting status).

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In addition to the inferential analysis, LDL cholesterol and LDL cholesterol change from baseline will be reported descriptively by visit for fasted values. The average of weeks 12-28 will also be reported.

Residual plots will be produced showing the following:

- Model residuals in the y-axis and model predictions in the x-axis,
- Model residuals in the y-axis and baseline LDL-cholesterol in the x-axis.

7.4.2.3 Use and time to first use rescue therapy during the treatment period [composite of RBC transfusions, IV iron supplementation and rescue ESA]

Time to first use of rescue therapy will also be analyzed similarly as in Section 7.4.2.7 except that only superiority will be tested and will be declared if the upper bound of the two-sided 95% confidence interval of the hazard ratio of the two treatment arms is below 1.

In addition, the number and percentage of subjects with rescue therapy during the Efficacy Emergent Period will be reported by treatment group.

Table 19 Primary and sensitivity analysis for use and time to first use rescue therapy

Code	Set	Endpoint	Method	Covariates
Primary	FAS	Time to first use rescue therapy	Cox regression + Kaplan Meier	Stratified on Region, History of CV and adjusted on BL Hb, BL eGFR as continuous covariates
S1	All Randomized	Time to first use rescue therapy	Cox regression + Kaplan Meier	Stratified on Region, History of CV and adjusted on BL Hb, BL eGFR as continuous covariates
S2	FAS	time to first use rescue therapy	Cox regression + survival curve (Breslow estimator) using IPCW method	Stratified on Region, History of CV and adjusted on BL Hb, BL eGFR as continuous covariates

For the IPCW method, refer to Appendix 10.7 for details. If the conclusions of the analysis using stratified cox model and IPCW method are not concordant, additional analysis using IPCW method will performed for each of the endpoints separately.

- Time to first use of RBC transfusion
- Time to first use of IV iron supplementation
- Time to first use of ESA

Details of these endpoints are provided in Sections 7.4.3.8, 7.4.3.9 and 7.4.3.10

7.4.2.4 Change from baseline in SF-36 VT subscore to the average in weeks 12–28

Change from baseline in VT subscore of SF-36 to the average of weeks 12–28 will be compared by treatment arm for all subjects (primary analysis) and in the subsets of subjects with baseline vitality subscore below 50 and equal or above to 50. It will be done using a MMRM method adjusting for the region, history of CV, baseline SF-36 VT subscore,

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baseline Hb and baseline eGFR as covariates. Baseline SF-36 VT subscore, baseline Hb and baseline eGFR will be included as continuous variables.

The analysis will be similar to the analysis provided in Section 7.4.1.2 Superiority will be declared if the lower bound of the two-sided 95% confidence interval of the difference between roxadustat and placebo is above 0.

The analysis will be done on the FAS.

Table 20 Primary and sensitivity analysis for change from BL in SF-36 VT subscore to the average in weeks 12 to 28

Code	Set	Endpoint	Method	Covariates
Primary	FAS	SF36-VT Change from Baseline at Weeks 12-28 for all subjects	MMRM	Region, History of CV, visits and visits by treatment as categorical variables. BL Hb, BL SF-36 VT subscore and BL eGFR as continuous covariates.
S1	FAS	SF36-VT Change from Baseline at Weeks 12-28 for subjects with BL VT subscore below 50	MMRM	Region, History of CV, visits and visits by treatment as categorical variables. BL Hb, BL SF-36 VT subscore and BL eGFR as continuous covariates.
S2	FAS	SF36-VT Change from Baseline at Weeks 12-28 for subjects with BL VT subscore equal or above 50	MMRM	Region, History of CV, visits and visits by treatment as categorical variables. BL Hb, BL SF-36 VT subscore and BL eGFR as continuous covariates.

Residual plots will be produced showing the following:

- Model residuals in the y-axis and model predictions in the x-axis,
- Model residuals in the y-axis and baseline SF-36 VT subscore in the x-axis.

In addition to the inferential analyses, SF-36 VT and SF-36 VT change from baseline will be reported descriptively by visit, using all available data. The average of weeks 12-28 will also be reported.

7.4.2.5 Change from BL in SF-36 Physical Functioning (PF) sub-score to the average PF sub-score of weeks 12 to 28

Change from baseline in PF subscore of SF-36 to the average of weeks 12–28 will be compared by treatment arm for all subjects (primary analysis) and in the subsets of subjects with baseline PF subscore below 35 and equal or above 35. It will be done using a MMRM method adjusting for the region, history of CV, baseline SF-36 PF subscore, baseline Hb and baseline eGFR as covariates. Baseline SF-36 PF subscore, baseline Hb and baseline eGFR will be included as continuous variables.

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The analysis will be similar to the analysis provided in Section 7.4.1.2 Superiority will be declared if the lower bound of the two-sided 95% confidence interval of the difference between roxadustat and placebo is above 0.

The analysis will be done on the FAS.

Table 21 Primary and sensitivity analysis for change from BL in SF-36 Physical Functioning (PF) sub-score to the average PF sub-score of weeks 12 to 28 for all subjects

Code	Set	Endpoint	Method	Covariates
Primary	FAS	SF36-PF Change from Baseline at Weeks 12- 28 for all subjects	MMRM	Region, History of CV, visits and visits by treatment as categorical variables. BL Hb, BL SF-36 PF subscore and BL eGFR as continuous covariates.
S1	FAS	SF36-PF Change from Baseline at Weeks 12- 28 for subjects with BL PF subscore below 35	MMRM	Region, History of CV, visits and visits by treatment as categorical variables. BL Hb, BL SF-36 PF subscore and and BL eGFR as continuous covariates.
S2	FAS	SF36-PF Change from Baseline at Weeks 12- 28 for subjects with BL PF subscore equal or above 35	MMRM	Region, History of CV, visits and visits by treatment as categorical variables. BL Hb, BL SF-36 PF subscore and BL eGFR as continuous covariates.

Residual plots will be produced showing the following:

- Model residuals in the y-axis and model predictions in the x-axis,
- Model residuals in the y-axis and baseline SF-36 PF subscore in the x-axis.

In addition to the inferential analyses, SF-36 PF and SF-36 PF change from baseline will be reported descriptively by visit, using all available data. The average of weeks 12-28 will also be reported.

7.4.2.6 Change from BL in mean arterial pressure (MAP) to the average MAP value of weeks 20 to 28

The blood pressure effect is shown by use of the change from baseline in MAP.

MAP change from baseline to the average MAP value in weeks 20-28 will be analyzed using a MMRM model as in Section 7.4.1.2.1 (with the addition of MAP at baseline as continous covariate). The analysis will be done on the PPS.

For missing MAP imputation rules, refer to Section 7.11.1

Non-inferiority can be concluded if the upper bound of the two-sided 95% CI of the difference between roxadustat and placebo (roxadustat minus placebo), calculated on the PPS is below 2 mm Hg.

An additional analysis (not part of the sequence) will be done on the All Randomized.

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Table 22 Primary and sensitivity analysis for the MAP change from BL to the average MAP in weeks 20-28

Code	Set	Endpoint	Method	Covariates
Primary	PPS	Change from baseline to the Average MAP in weeks 20-28	MMRM	Region, History of CV, visits and visits by treatment as categorical variables. BL MAP, BL Hb and BL eGFR as continuous covariates.
S1	All Randomized	Change from baseline to the Average MAP in weeks 20-28	MMRM	Region, History of CV, visits and visits by treatment as categorical variables. BL MAP, BL Hb and BL eGFR as continuous covariates.

In addition to the inferential analyses, MAP and MAP change from baseline will be reported descriptively by visit, using all available data. The average of weeks 20-28 will also be reported.

Residual plots will be produced showing the following:

- Model residuals in the y-axis and model predictions in the x-axis,
- Model residuals in the y-axis and baseline MAP in the x-axis.

7.4.2.7 Time to first occurrence of hypertension (defined as either SBP ≥170 mmHg AND an increase from BL ≥ 20 mmHg or as DBP ≥ 110 mmHg, AND an increase from BL ≥ 15 mmHg)

Time to first occurrence of an increase in blood pressure, including time to censoring, defined in Section 6.1.2.7 will be used in a Cox Proportional Hazards regression analysis, to compare treatment arms, stratified for region and history of CV and adjusted for baseline eGFR and baseline Hb (both continuous), and provide hazard ratio and their 95% confidence intervals.

Non-inferiority will be declared if the upper bound of the 2-sided 95% confidence interval of the hazard ratio (roxadustat as relative to placebo), calculated on the PPS, is below 1.3. As per Table 16 once the null hypothesis is rejected, superiority will be checked for this variable on the FAS, as part of the fixed sequence testing procedure. Superiority will be concluded if the upper bound of the two-sided 95% CI of the hazard ratio of the two treatment arms (roxadustat as relative to placebo) is below 1.

The stratified Cox Model can be written:

$$\lambda_{i}(t; \underline{x}) = \lambda_{0i}(t) \exp(\alpha z)$$

where

i - indicator for stratum

z – treatment indicator – which is either roxadustat or placebo

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The SAS procedure for the Cox regression will be similar to the following:

```
proc phreg;
  model time_to_event*cens_var(1) = treatment Hb_Bas eGFR_bas / rl;
  strata CVHist Region;
run;
```

The SAS procedure for the Cox regression using IPCW method uses above similar code with weight statement. Refer to Appendix 10.7 for details.

Table 23 Primary and sensitivity analysis for the time to first occurrence of hypertension

Code	Set	Endpoint	Method	Stratas/Covariates
Primary	PPS	time to first occurrence of hypertension	Cox regression + Kaplan Meier	Stratified on Region and History of CV, and adjusted on BL Hb, BL eGFR as continuous covariates
S1	All Randomized	time to first occurrence of hypertension	Cox regression + Kaplan Meier	Stratified on Region, History of CV and adjusted on BL Hb, BL eGFR as continuous covariates
S2	FAS	time to first occurrence of hypertension	Cox regression + Kaplan Meier	Stratified on Region, History of CV and adjusted on BL Hb, BL eGFR as continuous covariates

In addition, the cumulative incidence curve of subjects with an increase in blood pressure from baseline will be plotted by treatment arm.

The cumulative incidence will be calculated as one minus the Kaplan-Meier estimate of the survival function. Two types of analyses can be performed: modeling the cause specific hazard or modeling the hazard of the sub-distribution. The first approach has been chosen in this SAP, because competing risks are assumed not to exist, since the main interest is to study the treatments effect and this method provides results to be generalized across datasets with different competing risks. One minus the Kaplan-Meier estimate can be interpreted as the probability that an event of interest occurs to a subject by time t, in the absence of any competing risk.

In addition to the cumulative incidence plot, the cumulative incidence at 3, 6 and 9 months with the 95% confidence interval will be reported using Greenwood's formula.

Model checking

The proportional hazards assumption will be checked graphically using a log-cumulative hazard plot against log-survival time. This plot will give approximately parallel lines if the proportional hazards assumption between treatment arms subgroups holds. This plot will be provided as part of the raw SAS outputs.

In addition, the number and percentage of subjects with an increase from baseline in blood pressure during the Safety Emergen Period will be reported by treatment arm (roxadustat and placebo) on the PPS. For subjects who have experienced more than one increase in blood pressure, only their first event following study treatment will be used in the analysis.

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run;

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In addition, the incidence rate (per 100 subject years at risk) will be calculated as follows:

```
Number of subjects with event
Total cumulative time at risk (years)
```

Where Total cumulative time at risk is the sum of individual time at risk defined as either time to occurrence of the event or time to censoring for subjects with no event.

Number of subjects at risk is defined as the number of subjects with (censored or non-censored) times to the event of interest greater or equal to t.

7.4.2.8 Rate of progression of CKD measured by annualized eGFR slope over time

Geometric Mean (GM) and coefficient of variation (CV) will be displayed for eGFR. In addition, change from baseline and 95% CI will be presented.

The annualized eGFR slope over time (expressed in ml/min per 1.73 m² or % per year) will be determined using the SAS code below:

```
proc mixed data=eqfr2;
class usubjid strata except egfr hb TRTPN TRTP;
model aval= strata except egfr hb HGBBL atptn
HGBBL*atptn egfrbl*atptn atptn*TRTPN*TRTP
atptn*strata except egfr Hb / solution ddfm=kr
outpredm=pred cl;
random intercept atptn / subject=usubjid type=un ;
estimate 'Annnualized slope Roxadustat'
    intercept 0
    strata except egfr hb 0 0 0 0
    HGBBL 0
     atptn 1
    HGBBL*atptn &meanHbBase
    egfrbl*atptn &mean egfrbl
    atptn*TRTPN*TRTP 1 0
    atptn*strata except egfr Hb &prop strata
  /cl;
estimate 'Annnualized slope Placebo'
    intercept 0
    strata except egfr hb 0 0 0 0
    HGBBL 0
     atptn 1
    HGBBL*atptn &meanHbBase
    egfrbl*atptn &mean egfrbl
     atptn*TRTPN*TRTP 0 1
     atptn*strata except egfr Hb &prop strata
  /cl;
ods output lsmeans=lsmeans un estimates=est un;
ods output FitStatistics=FitStatistics SolutionF=SolutionF;
```

Annualized eGFR slope over time is estimated by a random slopes and intercepts model using all available eGFR values (one baseline and all post-treatment values up to End of Treatment Period or start of dialysis) adjusted on Baseline Hb, Region, CV history at

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Baseline and the interaction terms (Baseline eGFR by timepoint and Baseline Hb by timepoint). All assessments collected after initiation of acute or chronic dialysis will be excluded from the analysis.

Superiority will be declared if the lower bound of the two-sided 95% confidence interval of the difference in Least Square Means between roxadustat and placebo is above 0.

Model checking:

Residual plots will be produced showing the following:

- Model residuals in the y-axis and model predictions in the x-axis,
- Model residuals in the y-axis and baseline Hb in the x-axis.

Different dot styles will be used for the two treatment arms. Solid black symbols (square) will be used for roxadustat and non-solid red symbols (X) will be used for placebo.

If the residual diagnostics show heteroscedasticity, additional analysis will be performed where annualized eGFR slope over time (% per year) is estimated by a random slopes and intercepts model using all available (log-transformed) eGFR values (one baseline and all post-treatment values up to End of Treatment Period or start of dialysis) adjusted on Baseline Hb, Region, CV history at Baseline and the interaction terms (Baseline log(eGFR) by timepoint and Baseline Hb by timepoint).

Least Square Means will be transformed back to the original scale and expressed as annual percent changes.

7.4.2.9 Additional Analyses of the Key Secondary Endpoints

Each of these key secondary endpoints will also be analyzed by the subgroups of interest defined in Section 7.8 using only the primary analysis method, descriptively (no hypothesis testing).

 Table 24
 Additional Analyses of the Key Secondary Endpoints

Code	Set	Endpoint	Method	Covariates
Al	FAS	Change to the Average Hb in weeks 28-36 (without rescue therapy) by Subgroup	MMRM	Region, History of CV, visits and visits by treatment as categorical variables. BL Hb and BL eGFR as continuous covariates.
A2	FAS	Change from baseline to the Average LDL in weeks 12-28 by Subgroup	MMRM	Region, History of CV, visits and visits by treatment as categorical variables. BL LDL, BL Hb and BL eGFR as continuous covariates.
A3	FAS	SF36-PF Change from Baseline at Weeks 12- 28 for all subjects by Subgroup	MMRM	Region, History of CV, visits and visits by treatment as categorical variables. BL Hb, BL SF-36-PF subscore and BL eGFR as continuous covariates.
Table continued on next page				

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Code	Set	Endpoint	Method	Covariates
A4	FAS	SF36-VT Change from Baseline at Week 28 for all subjects by Subgroup	MMRM	Region, History of CV, visits and visits by treatment as categorical variables. BL Hb, BL SF-36-VT subscore and BL eGFR as continuous covariates.
A5	PPS	Change from baseline to the Average MAP in weeks 20-28 by Subgroup	MMRM	Region, History of CV, visits and visits by treatment as categorical variables. BL MAP, BL Hb and BL eGFR as continuous covariates.
A6	PPS	time to first occurrence of hypertension by Subgroup	Cox regression + Kaplan Meier	Stratified on Region, History of CV and adjusted on BL Hb, BL eGFR as continuous covariates

^{*} Subgroup: (1) age, (2) sex, (3) region, (4) baseline hemoglobin category, (5) history of CV (6) Baseline eGFR category (7) Baseline CRP category [only for A1] and (8) Baseline Iron Repletion Status category [only for A1]

Forest plots will be produced where all subgroup factors will appear in the y-axis and the appropriate statistic comparing roxadustat to placebo and the 95% confidence interval will appear in the x-axis.

7.4.3 Analysis of Additional Secondary Efficacy Endpoints

All the analyses below will be superiority tests. These inferential analyses will be performed on the FAS and presented treatment effect as Roxadustat versus placebo.

Descriptive statistics will be presented by treatment arm.

7.4.3.1 Hb level averaged over weeks 28 to 36, 44 to 52, and 96 to 104 without use of rescue therapy within 6 weeks prior to and during these 8-week evaluation periods

Averaged Hb over weeks 28-36, 44 to 52 and 96 to 104 will be described by treatment arm on the FAS.

The SAS procedure will be similar to the one provided in Section 7.4.2.1

In addition, the number and proportion of subjects with average Hb over weeks 28-36 and over weeks 44-52 and 96-104 and by visit within the <10 g/dL, 10-12 g/dL and >12 g/dL categories will be reported.

7.4.3.2 Time to achieve the first Hb response as defined by primary endpoint for EU (EMA)

Time to achieve the first Hb response, without rescue therapy, will be analyzed using the same methods described in Section 7.4.2.7, on the FAS.

Superiority will be declared if the lower bound of the two-sided 95% confidence interval of the hazard ratio is above 1.

Cumulative incidence will be provided at 4, 8, 16, and 24 weeks with their associated 95% confidence interval reported using Greenwood's formula.

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7.4.3.3 Hb change from BL to each post-dosing time point

Hb value and change from BL Hb to each post dosing time point will be described by treatment arm on the FAS.

The analysis and SAS procedure will be the same as in Section 7.4.2.1

7.4.3.4 Hb change from BL to the average Hb value of weeks 28 to 36, 44 to 52, and 96 to 104 regardless of the use of rescue therapy

The analysis will be done similarly as in Section 7.4.2.1 on the FAS except that it will be for weeks 28-36, 44-52 and 96-104.

7.4.3.5 Categorical analysis for Hb values

Proportion of Hb values:

The proportion of Hb values within 10-12 g/dL or ≥ 10 g/dL is a quantitative variable in the 0-100 range for each subject. Descriptive statistics for this variable will be presented by treatment arm. This variable will be presented in weeks 28-36, in weeks 44-52 and in weeks 96-104, on the FAS.

Percentage of time during the Efficacy Emergent Period:

Descriptive statistics for the percentage of time with Hb values falling in each interval interval (<10.0 g/dL, within 10.0-12.0 g/dL, > 12.0 g/dL, > 10.0 g/dL, > 13.0 g/dL and > 14.0 g/dL) between the first and last Hb assessement during the Efficacy Emergent Period will be presented by treatment arm.

The number and percentage of subjects, and the number of events, will be reported based on Hb values from the central lab with Hb increase by >2.0 g/dL between any two visits within 4 weeks of treatment.

Time to first occurrence of potential EH will also be analyzed similarly as in Section 7.4.2.7 (except that all data during the Efficacy Emergent Period will be taken into account for the analysis). The results will be presented by period (First 6 weeks, Week 7 - Week 27, Week 28 - Week 52 and > Week 52)

7.4.3.6 Occurrence (number) of hospitalizations, number of days of hospitalization per PEY and time to first hospitalization

The number and percentage of subjects with hospitalization will be reported. Descriptive statistics and frequency tabulations by treatment arm of the total duration of hospitalization (days), the average duration of each hospitalization (days), the number of hospitalizations, number of days of hospitalization per PEY and reason for hospitalization will also be reported.

Time to first hospitalization will also be analyzed similarly as in Section 7.4.2.7 (except that all data during the Efficacy Emergent Period will be taken into account for the analysis).

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Superiority will be declared if the upper bound of the two-sided 95% confidence interval of the hazard ratio of the two treatment arms is below 1. Both descriptive summary and time to first hospitalization will be reported by eGFR category ($<15 \text{ vs} \ge 15$).

As a sensitivity analysis, the above analysis will be repeated using IPCW method (Appendix 10.7).

The analysis will be done on the FAS.

7.4.3.7 Occurrence and time to first use of rescue therapy during the First 24 Weeks [composite of RBC transfusions, IV iron supplementation and rescue ESA]

The number and percentage of subjects with rescue therapy during the first 24 weeks will be reported by treatment arm.

Time to first use of rescue therapy will also be analyzed similarly as in Section 7.4.2.7 (except that all data during the Efficacy Emergent Period will be taken into account for the analysis).

The analysis will be done on the FAS.

Superiority will be declared if the upper bound of the two-sided 95% confidence interval of the hazard ratio of the two treatment arms is below 1.

7.4.3.8 Occurrence and time to first use of RBC transfusions, number of RBC packs per subject, volume of RBC transfused per subject

The number and percentage of subjects with RBC transfusion will be reported. Descriptive statistics by treatment arm for number of RBC packs and volume of blood transfused will be reported. Time to first use of RBC transfusion will be analyzed during the Efficacy Emergent Period similarly as in Section 7.4.2.7

Mean monthly number of RBC packs and volume of RBC transfused during the Efficacy Emergent Period will be compared by treatment arm using a ANCOVA model as in Section 7.4.1.2.1 (except that no multiple imputation will be performed). Subjects with no medication record of RBC will be assumed that they received no RBC and therefore number of packs and volume will be set to 0. The number and percentage of subjects with number of RBC Packs/Volume >0 will be presented. The analysis will be done on the FAS.

Superiority will be declared if the upper bound of the two-sided 95% confidence interval of the hazard ratio of the two treatment arms is below 1.

7.4.3.9 Occurrence and time to first use of IV iron supplementation. Mean monthly IV iron (mg) per subject during day 1 to week 36, weeks 37-52 and weeks 53-104 (monthly defined as a period of 4 weeks)

The number and percentage of subjects who received IV Iron and the total amount of IV Iron used during the Efficacy Emergent Period will be reported descriptively by treatment arm.

The incidence and cumulative incidence of subjects receiving IV Iron will be calculated similarly as in Section 7.4.2.7

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Mean monthly IV iron (mg) per subject during day 1 to week 36, weeks 37-52 and weeks 53-104 will be summarized by treatment arm. Subjects with no medication record of IV Iron will be assumed that they received no IV Iron (for patients under treatment during that month).

The analysis will be done on the FAS.

Furthermore, the total amount of IV Iron used during the efficacy emergent period as well as for Day 1 to week 36, weeks 37 to 52 and weeks 53 to 104.

Time to first use of IV iron will also be analyzed similarly as in Section 7.4.2.7

Superiority will be declared if the upper bound of the two-sided 95% confidence interval of the hazard ratio of the two treatment arms is below 1.

7.4.3.10 Occurrence and time to first use of ESA. Number of ESA-Week per year

The number and percentage of subjects with ESA use as rescue therapy, and the number of ESA-weeks/year will be reported descriptively by treatment arm.

Time to first use of ESA will also be analyzed similarly as in Section 7.4.2.7 (except that all data during the Efficacy Emergent Period will be taken into account for the analysis).

The analysis will be done on the FAS.

Superiority will be declared if the upper bound of the two-sided 95% confidence interval of the hazard ratio of the two treatment arms is below 1.

7.4.3.11 Change from BL to each post-dosing study visit in Total cholesterol, LDL/High-density Lipoprotein (HDL) ratio, Non-HDL cholesterol, Apolipoproteins A1 and B, ApoB/ApoA1 ratio

Descriptive statistics (value, change from baseline) by visit and treatment arm. Descriptive statistics will also be reported regardless of fasting status.

7.4.3.12 Occurrence of mean LDL cholesterol <100 mg/dL calculated over weeks 12 to 28

The number and percentage of subjects with mean LDL cholesterol less than 100 mg/dL (fasting values and regardless fasting status) on average in weeks 12-28 will be reported by treatment arm and by baseline value.

7.4.3.13 Occurrence of achieved antihypertensive treatment goal in CKD subjects (SBP< 130 mmHg and DBP< 80 mmHg) based on the mean SBP and mean DBP calculated over weeks 12 to 28.

The number and percentage of subjects with achieved antihypertensive treatment goal over an evaluation period defined as the average of available values in weeks 12-28 will be reported by treatment arm.

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7.4.3.14 Health related Quality of Life Questionnaires Change from BL to the average value of weeks 12 to 28

The following questionnaires will be analyzed:

- SF-36 (Physical Component Score (PCS));
- FACT-An (Anemia Subscale ("Additional Concerns"), Total FACT-An Score);
- EQ-5D 5L (VAS Score);
- Work Productivity and Activity Impairment Questionnaire: Anemic Symptoms (WPAI:ANS).

SF-36 and FACT-An

Descriptive statistics (value, change from baseline) will be presented for SF-36 (subscale and component scores) and FACT-An (total and subscale scores) by visit and treatment arm. Mean values will also be plotted over time and by treatment arm.

In addition, for the average value in weeks 12-28, an inferential analysis, similar to the one defined in Section 7.4.2.1 will be performed for the following endpoints:

- Physical Component Scores of SF-36 (SF-36 PCS)
- Anemia Subscale ("Additional Concerns") of FACT-An Scores
- Total FACT-An Scores

For SF-36, at each visit, the frequency and proportion of subjects with a change from baseline <3/>= 3 points and <5/>=5 points will be reported for Physical Functioning, Vitality and Physical Component scores.

EQ-5D 5L

For the EQ-5D 5L VAS score, change from baseline to each visit and to the average of weeks 12-28 will be described by treatment arm.

For the 5 EQ-5D 5L qualitative domains, the number and percentage of subjects in each response level value will be reported by visit and treatment arm.

Work Productivity and Activity Impairment (WPAI)

The number and proportion of employed subjects will be reported by visit and treatment arm.

WPAI calculated variables will be summarized descriptively by visit and treatment arm.

Furthermore, change from baseline to each visit and to the average of weeks 12-28 and 36-52 will be described by treatment arm.

7.4.3.15 Patients' Global Impression of Change (PGIC)

Patients' Global Impression of Change will be summarized descriptively by visit and treatment arm.

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7.4.3.16 Hepcidin and Iron, HbA1c and CKD progression parameters

Changes from baseline to each study visit will be calculated for these parameters:

- Serum hepcidin
- Serum ferritin
- TSAT
- HbA1c level
- Fasting blood glucose
- Serum creatinine (log transformed)
- Albumin/creatinine ratio in urine (log-transformed)

Descriptive statistics and frequency tabulations will be presented for these parameters and for the change from baseline by visit and treatment arm. Mean values will also be plotted versus visit by treatment arm.

Geometric Mean (GM) and coefficient of variation (CV) will be displayed for serum creatinine and albumin/creatinine ratio in urine . In addition, GM Ratio from baseline and 95% CI will be presented these parameters by transforming the change from baseline of the log-transformed data back to the original scale.

All time to event endpoints as defined in Section 6.1.3.16 will be will be analyzed using the same methods described in Section 7.4.2.7 on the FAS. Superiority will be declared if the lower bound of the two-sided 95% confidence interval of the hazard ratio is above 1.

As a sensitivity analysis, the above stratified cox model will be repeated using IPCW method (Appendix 10.7) for the following endpoints:

• Time to CKD progression (composite of doubling serum creatinine, chronic dialysis or renal transplant, and Death)

If the conclusions of the analysis using stratified cox model and IPCW method are not concordant, additional analysis using IPCW method will performed for each of the following endpoints separately.

- Time to doubling of serum creatinine
- Time to chronic dialysis or renal transplant
- o Time to occurrence for a subject who died or chronic dialysis or renal transplant
- Time to at least 40% decrease in eGFR from baseline, chronic dialysis or renal transplant.
 If the conclusions of the analysis using stratified cox model and IPCW method are not concordant, additional analysis using IPCW method will performed for each of the following endpoint separately.
 - Time to at least 40% decrease in eGFR from baseline

A listing of dialysis data will also be provided.

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7.4.4 Analysis of Exploratory Variables: hs-CRP (High Sensitivity C-Reactive Protein) and sTFR (Soluble Transferrin Receptor)

For each visit, descriptive statistics with the absolute values and change from baseline for hs-CRP and sTFR will be displayed by treatment arm.

Genotyping will be shipped to a delegated CRO and analyzed under the responsibility of Bioanalysis-Europe of Astellas Pharma Europe B.V. A separate report will be provided.

7.5 Analysis of Safety

Safety analyses will be performed using the Safety Analysis Set (SAF).

Missing dates' imputation rules for AE onset date and stop date are detailed in Section 7.11.2

For each safety parameter, the last non-missing assessment prior to the first dose of study drug will be used as the baseline for all analyses, unless specified otherwise.

7.5.1 Adverse Events

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0. They will be summarized by System Organ Class (SOC) and Preferred Term (PT).

7.5.1.1 Overview

An overview table will include the following details, by treatment arm:

- Number and percentage of subjects with TEAEs,
- Number and percentage of subjects with causally drug related TEAEs,
- Number and percentage of subjects with serious TEAEs,
- Number and percentage of subjects with serious drug related TEAEs,
- Number and percentage of subjects with TEAEs leading to permanent discontinuation of study drug,
- Number and percentage of subjects with causally drug related TEAEs leading to permanent discontinuation of study drug,
- Number and percentage of subjects with NCI CTC Grade 3 or higher TEAEs,
- Number and percentage of subjects with TEAEs leading to death
- Number and percentage of subjects with drug related TEAEs leading to death and
- Number of deaths occurring during the Safety Emergent Period and overall.

7.5.1.2 Proportion of subjects with TEAEs by SOC/PT

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized by treatment arm. Summaries will be provided for:

- TEAEs
- TEAEs (by PT only)
- Drug related TEAEs,
- TEAEs with NCI CTC Grade 3 or higher
- TEAEs by severity

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- Drug related TEAEs by severity
- Serious TEAEs,
- Drug related serious TEAEs,
- TEAEs leading to permanent discontinuation of study drug,
- Drug related TEAEs leading to permanent discontinuation of study drug,
- TEAEs excluding serious adverse events that equal to or exceed a threshold of 5.0% in any treatment arm (roxadustat or placebo),
- TEAEs leading to death,
- Drug-related TEAEs leading to death,
- Common TEAEs that equal to or exceed a threshold of 5.0% in any treatment arm (roxadustat or placebo)
- TEAEs by relationship to the study drug,
- AEs occurring during the post study follow up period
- Serious AEs during the post-stiudy follow up period
- Onset of common (>=5% in Any treatment arm(roxadustat or placebo)) TEAEs by treatment duration: <3 months, ≥3 to ≤6 months, >6 to ≤12 months, >12 months

For the summaries by severity or relationship to the study drug,in the subject count, if a subject has multiple TEAEs with the same SOC or PT, but with different severity or relationship, then the subject will be counted only once with the worst severity and highest degree of relationship, however, if any of the severity or relationship values are missing then the subject will be counted only once with missing severity or relationship. In the adverse event count, the adverse events will be presented in each category they were classified to. Drug related TEAEs will be presented in a similar way by severity only.

Maximum severity or relationship will be defined as the worst severity and highest degree of relationship on-treatment (see Section $\boxed{6.2}$).

No queries will be done for SMQs.

7.5.1.3 Event-rates per 100 patient-years

The number of events and event rate (per 100 patient years) during the Safety Emergent Period with TEAEs, as classified by SOC and PT will be calculated by treatment arm. Summaries will be provided for:

- TEAEs
- TEAEs censored at start of chronic dialysis
- TEAE NCI CTC Grades 3 or higher
- Serious TEAEs,
- TEAEs leading to death.

7.5.1.4 Incidence rates and cumulative incidence

Since the percentage of adverse events might be different between treatment arms due to the difference in the discontinuation rates, in addition to the frequency tables above, the incidence rate (per 100 subject years at risk) and the cumulative incidence at 6 months, 12,

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18 months & 24 months with the 95% confidence interval, using Greenwood's formula, will be reported by treatment arm.

It will be done for each of the following event types of special interest:

- Serious TEAEs,
- TEAE for each SOC (>10% for a SOC in total SAF)
- Deaths occurring during the Safety Emergent Period,
- Any death (including post-study follow up period),
- Related serious TEAEs,
- AEs leading to discontinuation of study drug, and
- TEAE NCI CTC Grades 3 or higher.

Hazard ratios of each of the TEAE categories of special interest above will be computed by using Cox Proportional Hazards regression stratified on region and history of CV and adjusted on baseline Hb and baseline eGFR as continuous covariates. Hazard ratios (roxadustat as relative to placebo) and their 95% CI will be calculated for each TEAE category.

As a sensitivity analysis, the above analysis will be repeated using IPCW method (Appendix 10.7) for the following event types of special interest:

- Serious TEAEs,
- TEAE for each SOC (>10% for a SOC in total SAF)
- Deaths occurring during the Safety Emergent Period, and
- TEAE NCI CTC Grades 3 or higher.

A dot-and-forest plot will be produced showing each of the above TEAE categories on the y-axis. The incidence rates by treatment arm, the stratified Cox hazard ratios (roxadustat as relative to placebo) and their 95% CI will be shown on the x-axis.

In addition, cumulative incidence plots for subjects experiencing each of the TEAE categories above will be produced by treatment arm.

Incidence rate (per 100 subject years at risk) in each treatment arm by SOC and PT and the cumulative incidences by SOC will also be produced for the most common TEAEs (>=5% in total SAF). In addition, cumulative incidence plots of subjects experiencing at least one most common TEAEs in a SOC will be produced. A dot-and-forest plot will be produced showing each SOC in the y-axis and the incidence rates, the Cox hazard ratio and its 95% CI in the x-axis. The SOC will be sorted by the hazard ratio.

7.5.1.5 Sensitivity/Subgroup analyses

- Subgroups of interest:

The number and percentage of subjects reporting TEAEs in each treatment arm will be tabulated by SOC and PT for the subgroups of interest defined in Section 7.8

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- Baseline eGFR category ($< 15 \text{ vs} \ge 15$) only :

The following summaries will be provided by comparing Baseline eGFR categories (< 15 vs ≥ 15):

- Event rate per 100 patient-years for TEAEs by SOC and PT
- Incidence rate and cumulative incidence for serious TEAEs
- Incidence rate and cumulative incidence for deaths during the safety emergent period
- Incidence rate and cumulative incidence for drug-related serious TEAEs
- Incidence rate and cumulative incidence for AEs leading to discontinuation of study drug
- Incidence rate and cumulative incidence for TEAE NCI CTC Grades 3 or higher
 - <u>Incidence rate and cumulative incidence censoring events occurring on or after the</u> start of chronic dialysis:

The same analysis in incidence as described in Section 7.5.1.4 will be performed (i.e., incidence rate, hazard ratios, dot-and-forest plots and cumulative incidence plots) by censoring all data occurring at initiation of chronic dialysis (see Section 6.2.1.3 for more details regarding the definition of time to event and time to censoring):

It will be done for:

- Serious TEAEs
- Serious TEAEs by baseline eGFR category ($< 15 \text{ vs} \ge 15$)
- Deaths occurring during the Safety Emergent Period,
- Deaths occurring during the Safety Emergent Period by eGFR category ($< 15 \text{ vs} \ge 15$)
- Drug-related serious TEAEs,
- Drug-related serious TEAEs by eGFR category ($< 15 \text{ vs} \ge 15$)
- AEs leading to discontinuation of study drug,
- AEs leading to discontinuation of study drug by eGFR category ($< 15 \text{ vs} \ge 15$)
- TEAE NCI CTC Grades 3 or higher
- TEAE NCI CTC Grades 3 or higher by eGFR category ($< 15 \text{ vs} \ge 15$)
- Incidence rate for TEAE by SOC and most common PTs
- Cumulative incidence by SOC for most common PTs.

7.5.1.6 AEs within 7 days

Additional summaries or analyses with events to be considered restricted to any adverse event starting up to Analysis Date of Last Dose + 7 days:

- Overview summary table of subjects with AEs
- Number and percentage of subjects with AEs, as classified by SOC and PT
- Number and percentage of subjects with AEs leading to death, as classified by PT
- Incidence rate for serious AEs (i.e., incidence rate, hazard ratios, dot-and-forest plots and cumulative incidence plots as described in Section 7.5.1.4 will be provided)
- Incidence rate for AEs NCI CTC Grades 3 or higher (i.e., incidence rate, hazard ratios, dot-and-forest plots and cumulative incidence plots as described in Section 7.5.1.4 will be provided)

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Pre-specified adjudicated cardiovascular and thrombo-embolic events will be analyzed in meta-analyses across multiple phase 3 studies and compared between treatment groups (roxadustat versus control). The statistical method for this analysis pooling studies will be detailed in a Pooled Statistical Analysis Plan (pSAP). The results will be presented in a separate report.

All data will also be listed. All Adverse Events collected from site 70051 will be listed separately.

7.5.2 Clinical Laboratory Evaluation

Descriptive statistics for laboratory values (in SI units) and changes from baseline at each assessment time point and for the maximum and minimum on-treatment (i.e., during Safety Emergent Period) value will be presented by treatment arm and treatment for the quantitative laboratory parameters.

Maximum and minimum on-treatment values will be determined using all the original values and not the derived windows.

Shift tables and number and percentage of subjects with shift to low and shift to high will be reported by treatment arm for the quantitative laboratory parameters.

Box plots of quantitative laboratory values (in SI units) versus visit will be produced by treatment arm (two arms in one page).

A plot for each parameter of mean (+/- 95% CI) versus visit will be produced by treatment arm (two arms in one page).

Summary by visit for qualitative laboratory parameters will be provided by treatment arm.

All clinical laboratory data will also be listed.

Potentially clinically significant (PCS) laboratory abnormalities

For each potentially clinically significant (PCS) criterion defined in Section 6.2.3.1 the percentage of subjects with abnormalities by visit and at any moment during the Safety Emergent Period and who did not meet the criteria at baseline will be reported by treatment arm.

Incidence rate (per 100 subject years at risk) and the cumulative incidence at 6 months, 12, 18 months & 24 months with the 95% confidence interval using Greenwood's formula of PCS abnormalities will also be reported, using only subjects who did not meet the criteria at baseline, by treatment arm. Risk of PCS abnormalities will be compared using the same Cox model as used in Section 7.5.1 Hazard ratio and its 95% will be calculated for the frequency of roxadustat as relative to placebo. A dot-and-forest plot will be produced showing the PCS abnormalities above in the y-axis and the incidence rates, the Cox hazard ratio and their 95% CI in the x-axis.

In addition, cumulative incidence plots for subjects experiencing each PCS abnormality will be produced by treatment arm (two arms in one page).

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7.5.2.1 Liver function tests

Descriptive summary of PCS values in Liver Enzymes and Total Bilirubin will be provided as per Astellas standard TLB_005 and FFG_008.

In addition, a matrix scatter plot of Liver Enzymes and Bilirubin (as in Astellas standard FFG_009) will be plotted showing the maximum ALT, AST, ALP and total bilirubin during the Safety Emergent Period crossed against each other. Different dots will be used for roxadustat and placebo.

Individual displays of Liver Enzymes and Bilirubin parameters, listed in Section 6.2.3.1 will be reported for all subjects with ALT and / or AST > 3 x ULN or total bilirubin > 2 x ULN during Safety Emergent Period.

For subjects who require further liver function investigations, additional information will be collected and listed.

7.5.3 Vital Signs

Descriptive and changes from baseline for vital signs (systolic blood pressure, diastolic blood pressure, respiratory rate, weight and pulse) at each assessment time point and for the maximum and minimum on-treatment (i.e during Safety Emergent Period) value will be presented by treatment arm.

Maximum on-treatment value will be determined using all the original values and not the derived windows.

A plot for each parameter of mean (+/- 95% CI) versus visit will be produced by treatment arm (two arms in one page).

PCS Vital signs criteria (10 Combined) will be analyzed in the same way as explained in Section 7.5.2 for PCS laboratory abnormalities.

All vital signs data will also be listed.

7.5.4 Electrocardiograms (ECGs)

Descriptive and changes from baseline for ECG parameters (Pulse, PR Interval, RR Interval, QRS interval, QT interval, and QTc interval) at each assessment time point and for the maximum on-treatment (i.e during Safety Emergent Period) value will be presented by treatment arm.

Maximum on-treatment value will be determined using all the original values and not the derived windows.

The number and percentage of subjects with post-baseline PCS values (see Table 8) will be tabulated by treatment group. The percentages are to be calculated relative to the number of subjects with available baseline and at least one post-baseline assessment. The numerator will be total number of subjects with at least one post-baseline PCS ECG value. Shift tables may be presented.

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The following PCS QTc Criteria (both QTcB and QTcF):

- QTc > 500 msec
- Change from baseline in QTc > 60 msec

will be analyzed separately in the same way as explained in Section 7.5.2 for PCS laboratory abnormalities.

A plot for each parameter of mean (+/- 95% CI) versus visit will be produced by treatment arm (two arms in one page).

In addition, ECG parameters will be reported according to Astellas standards TEG_003 and TEG_004.

All ECG data will also be listed.

7.5.5 Pregnancies

A listing of pregnancy test results will be provided.

7.6 Analysis of PK

The statistical methods for PK data will be described in a separate analysis plan. Results of the population PK analysis will not be reported in the Clinical Study Report but in a separate population PK report.

Plasma concentration data of roxadustat will be listed.

7.7 Analysis of PD

Not Applicable.

7.8 Subgroups of Interest

Selected efficacy and safety endpoints will be summarized for the subgroups defined on the basis of the categorized variables listed below in Table 25

Table 25 Subgroups of interest

Grouping variables	Subgroups
Age group	< 65 years
	65 - 74 years
	≥ 75 years
Sex	Female
	Male
Region	Western Europe
	Rest of the World
Baseline Hb	$\leq 8 \text{ g/dL}$
	> 8 g/dL
History of cardiovascular, cerebrovascular or	Yes
thromboembolic diseases	No
Table continued on next page	

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Grouping variables	Subgroups
Baseline eGFR	< 30 mL/min/1.73m ²
	$\geq 30 \text{ mL/min/}1.73\text{m}^2$
Baseline eGFR ¹	< 15 mL/min/1.73m ²
	$\geq 15 \text{ mL/min}/1.73\text{m}^2$
Baseline CRP ²	≤ULN
	> ULN
Baseline Iron Repletion Status ²	(TSAT >= 20% and ferritin >= 100 ng/mL) vs (TSAT < 20% or ferritin < 100 ng/mL)
1: only for the two primary efficacy endpo	oints and also for selected AE summaries.
² only for the two primary efficacy endpo	oints and the key secondary endpoint on Hb (week 28- week 36)

7.9 Other Analyses

The current analysis plan is based on version 2.0 of the protocol. An exploratory analysis on Hb maintenance will be conducted in the sub-set of patients treated for at least 24 weeks under protocol version 1.0. The sub-set includes patients that discontinued treatment prior to Week 24 under protocol version 1.0. The pooled roxadustat arm will be seperated into 3 groups according to their randomized treatment: (TIW, BIW, QW). Tables with summary statistics by visit up to Week 24 will be derived for the Hb values and the average weekly prescribed dose by the 4 treatment groups (placebo, roxadustat TIW, roxadustat BIW, roxadustat QW). In addition, the change from baseline to the Hb value average over Weeks 12-24 (excluding rescue medication) will be analysed using the MMRM model using Hb and eGFR at baseline as co-variates. In addition, average weekly dose will be summarized by treatment arm by 4-weekly period until subject switched to protocol version 2.0.

7.10 Interim Analysis (and Early Discontinuation of the Clinical Study)

The study will have no interim analysis with statistical inference. Safety data and dosing decisions will be monitored on an ongoing basis. Ongoing review of safety data will be completed by an independent Data and Safety Monitoring Board (DSMB).

7.11 Handling of Missing Data, Outliers, Visit Windows, and Other Information

7.11.1 Missing Data

For relevant analyses without rescue therapy, for subjects who used rescue therapy, the reported Hb values after the initiation of rescue therapy will be set to missing (instead of the reported values) for 6 weeks from the start date of rescue therapy (or the end in case the duration of rescue therapy > 1 day).

The following imputations will be performed for the continuous endpoints, unless specified otherwise:

• An MMRM model will be run for the purpose of implicit imputation of missing data by using all the available information from the observed data via the within-patient correlation structure for continuous endpoints with inferential analysis.

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• An ANCOVA model with multiple imputations (MI) will also be run.

No imputations will be done for endpoints with no inferential analysis.

7.11.2 Missing Dates

As a general rule, the worst case scenario imputation rule is usually used. A start date is generally imputed to the first possible day, unless the available information in the partly missing date is equal to the one in the reference date. In this case, the substituted date is set to the reference date. An end date is generally imputed to the last possible day.

Completely missing dates will not be imputed.

Diagnosis of anemia, CKD and Targeted Medical History

The following rules will be applied to impute partially missing dates of diagnosis of Anemia, CKD and targeted medical history, as defined in Table 26 below.

Table 26 Definitions of the Analysis Date of Diagnosis of Anemia, CKD and Targeted Medical History

Reported Date (from the eCRF)	Analysis Date (Derived)
/MM/YYYY	01/MM/YYYY
//YYYY	01/01/YYYY
DD//, or	
/MM/, or	No imputation
//	

Previous or Concomitant medication:

For previous or concomitant medications, including rescue medications and chornic dialysis, partially missing start dates and/or stop dates will be imputed as defined in Table 27 and Table 28 below:

Table 27 Definitions of the Previous or Concomitant Medication Analysis Start Date

Reported Date (from the eCRF)	Analysis Date (Derived)
/MM/YYYY	01/MM/YYYY
//YYYY	01/01/YYYY
DD//, or	
/MM/, or	No imputation
//	

If the imputed start date is after the stop date, then the imputed start date will be one day prior to the stop date.

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Table 28 Definitions of the Previous or Concomitant Medication Analysis Stop Date

Reported Date (from the eCRF)	Analysis Date (Derived)
/MM/YYYY	31/MM/YYYY, or
	30/MM/YYYY, or
	29/MM/YYYY, or
	28/MM/YYYY
//YYYY	31/12/YYYY
DD//, or	
/MM/, or	No imputation
/	

AE Onset date

For adverse events, partially missing start dates and/or stop dates will be imputed as defined in Table 29 and Table 30 below:

 Table 29
 Definitions of the Analysis Adverse Event Onset Date

Reported Date	Date of First Drug Intake	Analysis Date (Derived)
/MM/YYYY	DD/MM/YYYY	
/02/2008	14/02/2008	14/02/2008*
/02/2008	14/02/2007	01/02/2008
/02/2008	14/02/2009	01/02/2008
//YYYY	DD/MM/YYYY	
//2008	14/02/2008	14/02/2008
//2008	14/02/2007	01/01/2008
//2008	14/02/2009	01/01/2008
DD//		
/MM/		No imputation
//		

^{*} If the month and year is the same as the month and year of first drug intake, use date of the first drug intake.

 Table 30
 Definitions of the Analysis Adverse Event End Date

Reported Date	Analysis Date (Derived) *	
/MM/YYYY	31/MM/YYYY or	
	30/MM/YYYY or	
	29/MM/YYYY or	
	28/MM/YYYY	
//YYYY	31/12/YYYY	
DD//, or		
/MM/, or	No imputation	
//		

^{*}Death has to be taken into consideration when calculating this.

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7.11.3 Outliers

As a general rule, all values, including outliers will be analyzed.

7.11.4 Visits Windows

The study protocol gives the overall study schedule and the permissible intervals for visits expressed as the number of days relative to the first study medication date (Day 1).

For all study assessments reported by visit, the value which assessment day is the latest collected within the corresponding analysis visit window will be used. If more than one value is collected that day, then the latest value will be used in the analysis.

Analysis Visit windows, as depicted in <u>Table 31</u> below, will be used for the following study assessments reported by visit:

- Central laboratory parameters (except Lipid Panel),
- Vital Signs,
- ECG parameters,
- Exposure.

Table 31 Analysis Visit Windows

CRF Visit	Target Day ^a	Analysis Visit Windows Actual Assessment Day	Analysis Visit
Screening		Day -42 to Day -1	Screening
Day 1	Day 1	Day 1	Baseline
Week 1	Day 7 * (Week #) + 1	Day 2 to Day 11	Week 1
Week 2	Day 7 * (Week #) + 1	Day 12 to Day 21	Week 2
Week 4 – 22	Day 7 * (Week #) + 1	[Target Day – 7, Target Day +6]	Week 4 - 22
Week 24	Day 7 * (Week #) + 1	[Target Day – 7, Target Day + 13]	Week 24
Week 28 – 100	Day 7 * (Week #) + 1	[Target Day – 14, Target Day + 13]	Week 28 - 100
Week 104/EOT (for completers)	Day 7 * (Week #) + 1	[Target Day – 14, Target Day + 28]	Week 104
EOT Visit (for premature discontinuations) or unscheduled (on-tretament)	NA	NA	Analysis Visit corresponding to the actual visit window
EOT + 2 Weeks Visit	14 Days after EOT visit day	NA	EOT + 2 weeks
EOS Visit	28 Days after EOT visit day	NA	EOS
Unscheduled	NA	Day of EOT+1, Day of EOT+20	EOT+2 weeks
Unscheduled	NA	Day of EOT+21, Day of EOT+31	EOS

^a: Relative to Day 1 (first dose date of study medication)

Analysis Visit windows, as depicted in <u>Table 32</u> below, will be used for the quality of life efficacy study assessments:

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Table 32 Analysis Visit Windows for QoL

CRF Visit	Target Day ^a	Analysis Visit Windows Actual Assessment Day	Analysis Visit
Day 1	Day 1	Day 1	Baseline
Week 8	Day 7 * (Week #) + 1	[Target Day – 14, Target Day + 13]	Week 8
Week 12	Day 7 * (Week #) + 1	[Target Day – 14, Target Day + 27]	Week 12
Week 28	Day 7 * (Week #) + 1	[Target Day – 28, Target Day + 27]	Week 28
Week 36	Day 7 * (Week #) + 1	[Target Day – 28, Target Day +27	Week 36
Week 52	Day 7 * (Week #) + 1	[Target Day – 56, Target Day + 83]	Week 52
Week 76	Day 7 * (Week #) + 1	[Target Day – 84, Target Day + 97]	Week 76
Week 104/EOT (for completers)	Day 7 * (Week #) + 1	[Target Day – 98, Target Day + 28]	Week 104
EOT Visit (for premature discontinuations)	NA	NA	Analysis Visit corresponding to the actual visit window
Unscheduled	NA	NA	Analysis Visit corresponding to the actual visit window

^a: Relative to Day 1 (first dose date of study medication)

Analysis Visit windows, as depicted in <u>Table 33</u> below, will be used for the Lipid Panel, including LDL cholesterol efficacy study assessment:

Table 33 Analysis Visit Windows for Lipid Panel

CRF Visit	Target Day ^a	Analysis Visit Windows Actual Assessment Day	Analysis Visit
Day 1	Day 1	Day 1	Baseline
Week 4	Day 7 * (Week #) + 1	Day 2 to Day 42	Week 4
Week 8	Day 7 * (Week #) + 1	[Target Day – 14, Target Day + 13]	Week 8
Week 12	Day 7 * (Week #) + 1	[Target Day – 14, Target Day + 27]	Week 12
Week 20	Day 7 * (Week #) + 1	[Target Day – 28, Target Day + 27]	Week 20
Week 28	Day 7 * (Week #) + 1	[Target Day – 28, Target Day + 27]	Week 28
Week 36	Day 7 * (Week #) + 1	[Target Day – 28, Target Day + 27]	Week 36
Week 44	Day 7 * (Week #) + 1	[Target Day – 28, Target Day + 27]	Week 44
Week 52	Day 7 * (Week #) + 1	[Target Day – 28, Target Day + 55]	Week 52
Week 68	Day 7 * (Week #) + 1	[Target Day – 56, Target Day + 55]	Week 68
Week 84	Day 7 * (Week #) + 1	[Target Day – 56, Target Day + 69]	Week 84
Week 104/EOT (for completers)	Day 7 * (Week #) + 1	[Target Day – 70, Target Day + 28]	Week 104
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CRF Visit	Target Day ^a	Analysis Visit Windows Actual Assessment Day	Analysis Visit
EOT Visit (for premature discontinuations)	NA	NA	Analysis Visit corresponding to the actual visit window
EOS Visit	NA	Last assessment between Day 2 and study termination day	EOS
Unscheduled	NA	NA	Analysis Visit corresponding to the actual visit window

^a: Relative to Day 1 (first dose date of study medication)

For the MMRM analyses, which requires one value per visit, one analysis Hb value for each planned visit will be used.

For the ANCOVA analyses, which use the average, all available values in the analysis windows will be used for the calculation.

7.11.5 End of Safety Emergent Period

The end of Safety Emergent Period will be defined as:

- *Minimum [Analysis date of Last Dose + 28 days , max(EOS Visit, Date of death))* in case Analysis date of Last Dose = Date of Last Dose
- Minimum [(Analysis date of Last Dose + 28 days, max(EOS Visit, Date of death)) in case Analysis date of Last Dose = Date of the End of Extended Treatment Visit (due to missing date of Last Dose) and the subject is treatment completer or discontinued due to any reason apart from Lost to follow up.
- Analysis date of Last dose in case Analysis date of Last Dose = Date of the End of
 Extended Treatment Visit (due to missing date of Last Dose) and the subject
 discontinued due to Lost to follow up.
- Analysis date of Last dose in case Analysis date of Last Dose = Date of last available assessment (due to missing date of last dose and date of the End of Extended Treatment Visit). In case a subject died, then Minimum [Date of last available assessment + 28 days, Date of death)].

With Analysis Date of Last Dose defined in Section 6.5.4

7.11.6 End of Efficacy Emergent Period

For all subjects, the end of Efficacy Emergent Period will be defined as:

- Minimum (Analysis date of Last Dose + 7 days, EOT Visit)

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8 DOCUMENT REVISION HISTORY

Version	Date	Changes	Comment/rationale for change
1.0	28-May- 2014	NA	Document finalized
2.0	21-January- 2016	Reduction of the number of sensitivity analyses for the secondary endpoints.	1) Due to harmonization with Fibrogen 060 study SAP and to limit the additional analyses .
		2) New ordering for the key secondary endpoints.	2) Due to the importance of the QoL endpoints and the harmonization with Fibrogen 060 study SAP.3) PPS definition has been
		3) Implementation of the Time to event approach for the PPS and adjustment of the relevant sections.	revised in order to limit the exclusion of data by using a time to event approach rather than creating one PPS set for each period of interest.
		4) Change from ITT to All Randomized as per Astellas standard. Definition remains unchanged.	4) Astellas standards requirement. 5) Decision agreed by the
		5) Use of the Safety Emergent Period (i.e last dose + 28 days) as evaluation period by default for the safety endpoints.	5) Decision agreed by the study team to use a consistent approach for all the safety endpoints by extending the evaluated period up to 28 days after last dose, which matched the AE analyses.
		6) Use of the Efficacy Emergent Period (i.e last dose + 7 days) as evaluation period by default for most of the efficacy time to event endpoints.	6) Decision agreed with the study team to use a
		7) Use of "Time to censoring" instead of "time at risk" for patient with no event for more	wording. Time to censoring is more appropriate.
		clarity. 8) Clarification of time to censoring for events evaluated during the Safety Emergent Period/Efficacy Emergent	8) Based on the new definitions of Efficacy/Safety Emergent period, time to censoring for all time to

Version	<u>Date</u>	<u>Changes</u>	Comment/rationale for change
		Period.	events have been updated accordingly.
		9) Time to PCS vital signs added.	9) Time to PCS were already planned for lab and ECG but not for Vital signs. Decision was taken to provide them as well.
		10) Time to PCS ECG focused to QTc instead of all ECG assessments.	10) Time to event for PCS ECG other than QTcF was considered not of interest.
		11) Additional censoring rules for the post-dialysis data (used for some time to event related to AEs).	11) In order to assess the impact of dialysis on incidence rates of AEs, sensitivity analyses will be conducted by censoring patients at the date of dialysis.
		12) Update regarding derivation of MAP values: average of the 3 measurements instead of 2 (now in line with FG SAP).	12) Using the average of all 3 measurments is more efficient and is consistent with Fibrogen 060 study SAP.
		13) Implementation of primary efficacy endpoint for FDA (change in Hb from baseline to the average level between week 28 and week 52) and description of statistical analyses including sensitivity analyses for missing data	13) This additional endpoint has been added in protocol amendment 1.0. Sensitivity analyses for missing data were added following FDA feedback on Fibrogen 060 study. Both Fiborgen and Astellas now in line regarding this endpoint.
		14) Implementation of time to first hospitalization, time to first occurrence of serum creatinine doubled, time to first potential EH (2 different criteria separately), time to dialysis.	14) Due to harmonization with Fibrogen 060 study SAP and the expected difference in treatment durations
		15) Reduction in the number of analyses of subgroup of interests.	15) Due to harmonization with Fibrogen 060 study SAP.

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		16) Addition of the analysis of percentage of time when Hb > 12, 13 or 14.	16) Due to harmonization with Fibrogen 060 study SAP.
		17) MMRM model added for number of RBC and volume of RBC during the treatment period.	17) The concept of percentage of time with high Hb values was implemented in order to account for differences in individual treatment durations.
		18) Removal of descriptive analysis on the categorical change form baseline in Total FACT-An Score.	18) Inferential analysis for RBC was missing in the v1.0.
		19) Removal of the descriptive analysis on change from day of first dialysis to week 4 and week 12 of dialysis for SF-36, FACT-AN scores, EQ-5D, WPAI.	19) Descriptive statistics for categorical change not necessary since analysis on absolute change already planned and considered sufficient.
		20) Updated rule for complete missing start date and end date for concomitant medications. In that case, the medication will be considered as both previous and concomitant instead of only concomitant. For the analysis of monthly IV Iron use, MMRM has been replaced by ANCOVA.	20) Exploratory summary statistics of SF-36, FACT-AN scores, EQ-5D, WPAI for patients on dialysis not required since this is a small subset of patients and not based on the randomized population.
		21) Additional tables run on group of subjects enrolled after protocol amendment implementation	21) Previous rule considered too conservative since a missing year of start is usually for previous medications than concomitant. Decision was taken to consider such medications as both previous and
			concomitant. 22) MMRM model for monthly IV Iron was not adapted due the data distribution. Since montly average will be

Version	Date	Changes		Comm	ent/rationale for change
					calculated, ANCOVA is more appropriate. Added in order to assess the impact of protocol amendment 1.0.
3.0	06- November- 2017	£	Removal of the reporting for date informed consent for genotyping and genotyping sample.	1)	Decision agreed by the study team.
		S	Number and percentage of subjects with drug related FEAEs leading to death added.	2)	Astellas standards requirement
		2 1 1	Use of SBP \geq 170 mmHg AND an increase from BL \geq 20 mmHg or as DBP \geq 110 mmHg, AND an increase from BL \geq 15 mmHg for the definition of hypertension.	3)	Due to harmonization with Fibrogen 060 study SAP.
		I	Use of the Safety Emergent Period as evaluation period to be considered a concomitant medication.	4)	Decision agreed by the study team.
			ATC codes for Iron-chelating agents were updated.	5)	The ATC codes in previous version were not correct as they actually did not cover the Iron supplementation agents
		/	Belarus was added in the list of countries for Region B.	6)	Protocol requirement.
		I	Use of the Efficacy Emergent Period as evaluation period to be considered for the definition of rescue therapy.	7)	Decision agreed with the study team to use a consistent approach for rescue therapy by extending the evaluated period up to 7 days after last dose.
		l G H	Removal of the criterion "at east one Hb value >13 g/dL during the Efficacy Emergent Period" for the definition of Potential Excessive Hematopoiesis (EH).	8)	Due to harmonization with Fibrogen 060 study SAP.

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Y CI SIOII	Dau	9) For the analysis of number of RBC packs and volume, MMRM has been replaced by ANCOVA	9) MMRM model for RBC packs and volume was not adapted due the data distribution. Since monthly average will be calculated, ANCOVA is more appropriate.
		10) Removal of the calculation of the amount of IV iron in monthly intervals during the Efficacy Emergent Period.	10) Decision agreed by the study team not to report Mean IV Iron for each month but only for the period of interest.
		11) Removal of the supplementary analysis for each post-dosing timepoint for subjects with mean LDL cholesterol less than 100 mg/dL. Average W12-W28 should be done for both regardless and fasting.	11) Decision agreed by the study team.
		12) Implementation of the derivation of the hospitalization duration. When hospitalization is ongoing, the date of end of the Efficacy Emergent Period will be used.	12) Decision agreed by the study team to be more accurate.
		13) Removal of other baseline factors including: Diabetes mellitus, age, gender, BMI, baseline eGFR, baseline CRP, ferritin, TSAT, CHr, Hypertension from ANCOVA with MI.	13) Due to harmonization with Fibrogen 060 study SAP.
		14) Update the calculation of the number of days of hospitalization per PEY as: Minimum ((Date of discharge, End of Efficacy Emergent Period) – Date of admission + 1)] / [(Duration of Efficacy Emergent Period.	14) Decision agreed by the study team to be consistent with the definition.
		15) No comparison for IV Iron between treatment arms.	15) Due to the very small number of subjects with IV Iron.

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		16) Figure added with the	16) Decision agreed by the
		comparison between central	study team to check the
		laboratory hemoglobin	differences between the
		(g/dL) and HemoCue	two methods.
		hemoglobin (g/dL).	
		17) Removal of the analysis for	17) Decision agreed by the
		subjects who have reached Hb	study team
		>= 11.0 g/dL prior to week 28.	
		18) For time to first occurrence of serum creatinine doubled compared with baseline, a subject will be counted with an event either for doubled serum creatinine or ESRD, whichever comes first. Otherwise, we censor at date of last nonmissing serum creatinine assessment during the Safety Emergent Period.	18) Decision agreed by the study team to be consistent with the definition for time to first occurrence of serum creatinine doubled compared with baseline.
		19) For WPAI scale, the number and proportion of employed subjects was summarized by visit and treatment arm.	19) Decision agreed by the study team to check the number of employed subjects by visit and treatment arm.
		20) Fatigue subscale score added for FACT-An questionnaire.	20) Descriptive statistics fatigue were added due to a request from Health Economics and Outputs Research Department.
		21) Time to All Deaths including Post study FU added.	21) Decision agreed by the study team.
		22) Time to AEs by eGFR categories (<15 vs ≥ 15 mL/min/1.73m ²) added.	22) Decision agreed by the study team.
		23) Number of events and event rate (per 100 patient years) during the Safety Emergent Period with TEAEs added.	23) Decision agreed by the study team to compare treatments in a fair way due to potential difference in exposure between the two arms.
		24) New sensitivity analysis (MMRM) for change to the	24) Decision agreed by the study team.

Version	Date	Changes	Comment/rationale for change
		average Hb in weeks 28-52 including all Hb values up to end of treatment visit. 25) Interaction term baseline*visit added to the main MMRM model for Hb analysis	25) Based on internal statistical guidance and check on model fit.
4.0	08-March- 2018	1) Two additional subgroup analyses [Baseline CRP category (≤ULN vs. > ULN)] and Baseline Iron Repletion Status category [(TSAT >= 20% and ferritin >= 100 ng/mL) vs. others] added for the primary efficacy endpoints and the key secondary efficacy endpoint in Hb (week 28 − week 36)	1) Baseline CRP group (CRP ≤ULN vs. CRP > ULN) is considered as a marker for inflammation which may affect treatment response. A subgroup analysis is added to explore the consistency of the effect of roxadustat on the Hb related primary efficacy parameters. Iron repletion status may affect treatment response and is added for consistency with Fibrogen 060 study SAP.
5.0	11-Jul- 2018	1) Time to Rescue Therapy during the first 24 weeks was replaced by Time to Rescue Therapy during the treatment period as Key Secondary Efficacy endpoint. Endpoint at 24 weeks was therefore considered as Other Secondary endpoint	1) Due to harmonization with Fibrogen 060 study SAP.
		2) VT and PF SF-36 scores have been switched in the hierarchical order of the key secondary endpoints	2) Due to harmonization with Fibrogen 060 study SAP.
		3) eGFR slope over time was added at the bottom of the list of key secondary endpoint 4) Details were added in All Randomized section regarding exclusion of subjects from site 70051 5) Additional analyses on adverse	 3) Due to harmonization with Fibrogen 060 study SAP. 4) Site 70051 was terminated due to GCP violations and it is now clearly mentioned in the population section that those subjects are excluded from all analysis set. 5) Due to harmonization

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Version	Date	Changes	Comment/rationale for change
		event were added considering events occouring up to last dose +_7 days (i.e OT-7) 6) Details regarding derivation of CV history were added in	with Fibrogen 060 study SAP. 6) To provide additional details about derivation.
		relevant section 7) Time to first dialysis was changed to Time to chronic dialysis or renal transplant	7) Due to harmonization with Fibrogen 060 study SAP.
5.0	18-Jul- 2018	Time to event endpoints: For the following endpoints (new or existing), IPCW analysis is added. Additional endpoints of interest are added as indicated by new. a. Rescue therapy: Time to first use of rescue therapy [composite of RBC transfusions, IV iron supplementation and rescue ESA] Time to first use of RBC transfusion Time to first use of IV iron supplementation Time to first use of ESA b. Hospitalization: Time to first hospitalization c. CKD progression: Time to CKD progression (composite of doubling serum creatinine, chronic dialysis or renal transplant, and Death) (new) Time to doubling serum creatinine (new) Time to chronic dialysis or renal transplant Time to chronic dialysis or renal transplant Time to chronic dialysis or renal transplant or occurrence for a subject who died (new) Time to at least 40% decrease in eGFR from baseline, chronic dialysis or renal transplant (new) Time to at least 40% decrease in eGFR from baseline, chronic dialysis or renal transplant (new) Time to at least 40% decrease in eGFR from baseline (new) d. Adverse Events: Time to serious TEAE Time to death Time to TEAE with grade 3 or higher Time to TEAE by SOC (>10% for a SOC in total SAF)	Due to harmonization with Fibrogen 060 study SAP.
5.0	18-Jul- 2018	Appendix 8 is added about inverse probability censoring weighted model	To provide details about inverse probability censoring weighted

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			model	
5.0	18-Jul-	Rate of progression of CKD measured	To perform log transformed	
	2018	by annualized eGFR slope over time:	analysis only if residual analysis	
		Analysis is updated to use non-log	indicates heteroscedasticity	
		transformed eGFR values.		
5.0	18-Jul-	A summary is added for onset of	To provide summary of common	
	2018	common (>=5% in Any Treatment	TEAEs by treatment duration.	
		Group) TEAEs by Treatment Duration:		
		$<$ 3 months, \ge 3 to \le 6 months, $>$ 6 to \le 12		
		months, >12 months		
5.0	02-Aug-	End point time to doubling of serum	To be consistent with Time to	
	2018	creatinine or ESRD is updated as	CKD progression Endpoint.	
		Time to doubling of serum creatinine or		
		chronic dialysis or renal transplant		

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10 APPENDICES

10.1 Appendix 1: SF-36 v2

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
V	•	•	•	V
<u>1</u>	2	3	4	5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now?</u>

	Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago	
1	▼		▼	▼ □ ₄	5	

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3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

		limited	Yes, limited a little	limited
a	<u>Vigorous activities</u> , such as running, lifting heavy objects, participating in strenuous sports	□1	□2	Пз
b	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	□1	🗆 2	<u>□</u> 3
С	Lifting or carrying groceries	□1	\square_2	
d	Climbing several flights of stairs	□1	□2,.	Дз
e	Climbing one flight of stairs	□1	\square_2	,, <u>,</u> 3
f	Bending, kneeling, or stooping	□1	2	,,Дз
g	Walking more than a mile ,,,,,	□1	□2	Дз
h	Walking several hundred yards	□1	2	3
i	Walking one hundred yards	□1.,	2	
j	Bathing or dressing yourself	□1	\square_2	

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4.	During the past 4 weeks, how much of the time have you had any of the
	following problems with your work or other regular daily activities as a
	result of your physical health?

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	Cut down on the <u>amount of time</u> you spent on work or other activities	🗆 1	□2	□ ₃	🗀 4	5
b	Accomplished less than you would like	🗆 1	🗆 2	🗆 з	🗆 4	5
С	Were limited in the kind of work or other activities	□1,,	🗆 2	Пз	🗆 4	5
d	Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort) .	□1	\square_2	□ ₃	🗆 4	5

5. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

		the time	the time	the time		the time
	,					
3	Cut down on the <u>amount of time</u> you spent on work or other activities	□1,.			4	5
6	Accomplished less than you would like					
С	Did work or other activities less carefully than usual	□1	🗆 2	🗆 3	🗀 4	5

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6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
V		•		V
1	\square_2	З	4	5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
_					
1	\square_2	3	4	5	6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
_	•	lacksquare	•	•
\square_1		3	4	5

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10.

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9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>...

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
			\blacksquare			
a	Did you feel full of life?	□1,,		□3.,	4	5
b	Have you been very nervous?	,□1	🗆 2	3	4	5
С	Have you felt so down in the dumps that nothing could cheer you up?	□1	🗆 2	🗆 з	🗆 4	5
d	Have you felt calm and peaceful?	□1		3	🗆 4	5
e	Did you have a lot of energy?	, □₁	D ₂	🔲 з	4	5
f	Have you felt downhearted and low?	□1,,	🗆 2	□₃	□4	5
g	Did you feel worn out?	□1	🗀 2	3	🗆 4	5
h	Have you been happy?	□1,,	2	🔲 з	🗆 4	5
i	Did you feel tired?	□1 ,.	2	🔲 з	🗆 4	5
<u>or</u>	iring the <u>past 4 weeks,</u> ho <u>emotional problems</u> inte th friends, relatives, etc.)	rfered wi		_		
	All of Most of the time		me of e time	A little of the time		lone of ne time

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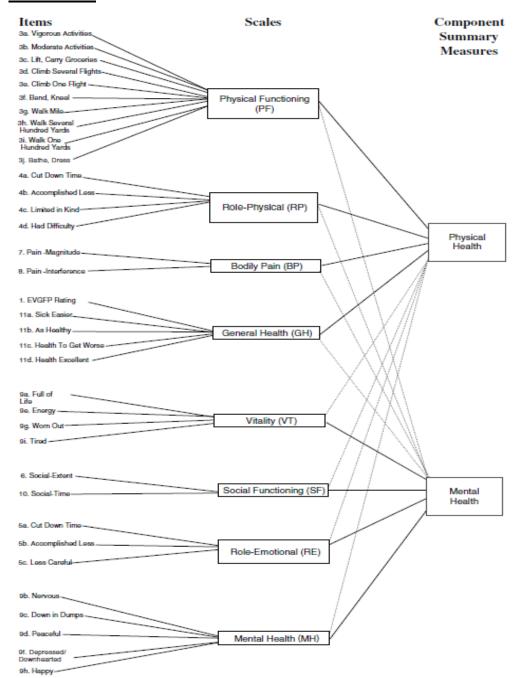
SF-36 v2

11. How TRUE or FALSE is each of the following statements for you?

		Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a	I seem to get ill more easily than other people	□1	🗆 2	🗆 3	□4 .	5
b	I am as healthy as anybody I know	□1,,	□₂	3.,	□₄ .	5
С	I expect my health to get worse	□1,,	□₂	🗆 3	□4 .	5
d	My health is excellent	□1	🗆 2	🗆 3		5

Thank you for completing these questions!

SF-36 Model



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10.2 Appendix 2: FACT-An (Version 4)

10.2.1 FACT-An Questionnaire

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	PHYSICAL WELL-BEING	Not at all	A little bit	Some- what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4
	SOCIAL/FAMILY WELL-BEING	Not at all	A little	Some- what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section.					
GS7	I am satisfied with my sex life	0	1	2	3	4

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FACT-An (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some- what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4
	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some- what	Quite a bit	Very much
GF1	FUNCTIONAL WELL-BEING I am able to work (include work at home)					
GF1 GF2		at all	bit	what	a bit	much
	I am able to work (include work at home)	at all	bit 1	what 2	a bit	much 4
GF2	I am able to work (include work at home) My work (include work at home) is fulfilling	at all 0	bit 1	what 2 2	a bit 3	much 4 4
GF2 GF3	I am able to work (include work at home) My work (include work at home) is fulfilling I am able to enjoy life	at all 0 0	bit 1 1	what 2 2 2	a bit 3 3	much 4 4 4
GF2 GF3 GF4	I am able to work (include work at home) My work (include work at home) is fulfilling I am able to enjoy life I have accepted my illness	at all 0 0 0 0 0	bit 1 1 1 1	what 2 2 2 2	a bit 3 3 3 3	4 4 4 4

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FACT-An (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some- what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble $\underline{\text{finishinq}}$ things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An9	I feel lightheaded (dizzy)	0	1	2	3	4
An10	I get headaches	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
An11	I have pain in my chest	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
An13	I am motivated to do my usual activities	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

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10.2.2 **FACT-An Scoring Guidelines**

- Instructions:* 1. Record answers in "item response" column. If missing, mark with an X
 - 2. Perform reversals as indicated, and sum individual items to obtain a score.
 - 3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale
 - 4. Add subscale scores to derive total scores (TOI, FACT-G & FACT-An).
 - 5. The higher the score, the better the QOL.

Subscale	Item Code	Reverse	item?	Item response	<u>Item Score</u>
PHYSICAL	GP1	4	-		=
WELL-BEING	GP2	4	-		=
(PWB)	GP3	4	-		=
	GP4	4	-		=
Score range: 0-28	GP5	4	-		=
Score range. 6 26	GP6	4	-		=
	GP7	4	-		=
				Sum individual iten	n scores:
				Multij	ply by 7:
			Divide	e by number of items an	ıswered:
				= <u>]</u>	PWB subscale score
SOCIAL/FAMILY	GS1	0	+		=
WELL-BEING	GS2	0	+		=
(SWB)	GS3	0	+		=
	GS4	0	+		=
Score range: 0-28	GS5	0	+		=
Score range. 0-28	GS6	0	+		=
	GS7	0	+		=
				Sum individual item	scores:
				Multip	oly by 7:
			Divide	by number of items an	swered:
				=	SWB subscale score
EMOTIONAL	GE1	4	_		=
WELL-BEING	GE2	0	+		=
(EWB)	GE3	4	_		=
(_ · · _ /	GE4	4	_		=
Score range: 0-24	GE5	4	_		=
	GE6	4	_		=
	0_0	-			
				Sum individual item	scores:
				Multip	oly by 6:
			Divide	by number of items an	
				=]	EWB subscale score

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FUNCTIONAL	GF1	0	+		=
WELL-BEING	GF2	0	+		=
(FWB)	GF3	0	+		=
	GF4	0	+		=
0.20	GF5	0	+		=
Score range: 0-28	GF6	0	+		=
	GF7	0	+		=
				Sum individual ite	em scores:

Sum individual item scores: _____ Multiply by 7: _____

Divide by number of items answered:

=FWB subscale score

Subscale	Item Code	Reverse ite	<u>m?</u>	Item response	<u>Item Score</u>
ANEMIA	HI7	4	_		=
SUBSCALE	HI12	4	-		=
(AnS)	An1	4	-		=
,	An2	4	-		=
C 0 00	An3	4	_		=
Score range: 0-80	An4	4	_		=
	An5	0	+		=
	An6	4	_		=
	An7	0	+		
	An8	4	'		
	An9	4	-		
		•	-		
	An10	4	-		=
	B1	4	-		=
	An11	4	-		=
	An12	4	-		=
	BL4	0	+		=
	An13	0	+		=
	An14	4	_		=
	An15	4	_		=
	An16	4	_		=
	1 11110	•			

Divide by number by tiems unswered.

=An Subscale score

To derive a FACT-An Trial Outcome Index (TOI):

Score range: 0-136

$$\frac{+}{(PWB \text{ score})} + \frac{+}{(FWB \text{ score})} + \frac{+}{(AnS \text{ score})} = \frac{-}{EACT-An \text{ TOI}}$$

To Derive a FACT-G total score:

Score range: 0-108

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To Derive a FACT-An total score:

Score range: 0-188

+ + + + + + = = =FACT-An Total score (PWB score) (SWB score) (EWB score) (FWB score) (AnS score)

FACIT-Fatigue Subscale Scoring Guidelines

- Instructions:* 1. Record answers in "item response" column. If missing, mark with an X
 - 2. Perform reversals as indicated, and sum individual items to obtain a score.
 - 3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
 - 4. The higher the score, the better the QOL.

Subscale Score	Item Code	Revers	se item?	<u>Item response</u>	<u>Item</u>
FATIGUE	HI7	4	-		=
SUBSCALE	HI12	4	-		=
	An1	4	-		=
	An2	4	-		=
Score range: 0-52	An3	4	-		=
<u> </u>	An4	4	-		=
	An5	0	+		=
	An7	0	+		=
	An8	4	-		=
	An12	4	-		=
	An14	4	-		=
	An15	4	-		=
	An16	4	-		=

Sum individual item scores:	
Multiply by 13:	
Divide by number of items answered:	
=Fatigue Subsca	le score

^{*}For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www.facit.org.

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10.3 Appendix 3: EQ-5D 5L v2

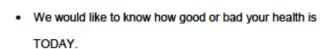
Under each heading, please tick the ONE box that best describes	your health TODAY
MOBILITY	
I have no problems in walking about	
I have slight problems in walking about	
I have moderate problems in walking about	
I have severe problems in walking about	
I am unable to walk about	
SELF-CARE	
I have no problems washing or dressing myself	
I have slight problems washing or dressing myself	
I have moderate problems washing or dressing myself	
I have severe problems washing or dressing myself	
I am unable to wash or dress myself	
USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)	
I have no problems doing my usual activities	
I have slight problems doing my usual activities	0 0 0
I have moderate problems doing my usual activities	
I have severe problems doing my usual activities	
I am unable to do my usual activities	
PAIN / DISCOMFORT	
I have no pain or discomfort	
I have slight pain or discomfort	
I have moderate pain or discomfort	0 0 0
I have severe pain or discomfort	
I have extreme pain or discomfort	
ANXIETY / DEPRESSION	_
I am not anxious or depressed	
I am slightly anxious or depressed	
I am moderately anxious or depressed	
I am severely anxious or depressed	Ц
I am extremely anxious or depressed	Ц

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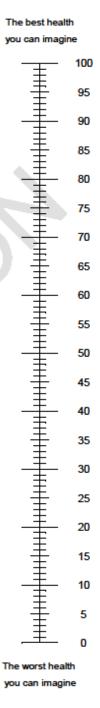
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EQ-5D 5L v2



- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
 0 means the <u>worst</u> health you can imagine.
- . Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =



3
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10.4 Appendix 4: WPAI:ANS V2.0

The following questions ask about the effect of your anaemic symptoms on your ability to work and perform normal daily activities. <i>Please fill in the blanks or circle a number, as indicated.</i>
1. Are you currently employed (working for pay)?NOYES If NO, tick "NO" and skip to question 6.
The next questions refer to the past seven days , not including today.
2. During the past seven days, how many hours did you miss from work because of problems associated with your anaemic symptoms? Include hours you missed on sick days, times you went in late, left early, etc., because of your anaemic symptoms. Do not include time you missed to participate in this study.
HOURS
3. During the past seven days, how many hours did you miss from work because of any other reason, such as annual leave, holidays, time off to participate in this study?
HOURS
4. During the past seven days, how many hours did you actually work?
HOURS (If "0", skip to question 6)
5. During the past seven days, how much did your anaemic symptoms affect your productivity while you were working?
Think about days you were limited in the amount or kind of work you could do days you

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual.

If anaemic symptoms affected your work only a little, choose a low number. Choose a high number if anaemic symptoms affected your work a great deal.

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WPAI:ANS

Consider only how much <u>anaemic symptoms</u> affected productivity while you were working.

												Anaemic
Anaemic												symptoms
symptoms had no												completely
effect on my work												prevented me
	0	1	2	3	4	5	6	7	8	9	10	from working

CIRCLE A NUMBER

6. During the past seven days, how much did your anaemic symptoms affect your ability to perform your normal daily activities, other than work at a job?

By normal activities, we mean the usual activities you perform, such as working around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could perform and times you accomplished less than you would like. If anaemic symptoms affected your activities only a little, choose a low number. Choose a high number if anaemic symptoms affected your activities a great deal.

Consider only how much <u>anaemic symptoms</u> affected your ability to do your normal daily activities, other than work at a job.

Anaemic symptoms												completely
had no effect on my daily activities						_	_	_				prevented me from doing my daily
	0	1	2	•	-	•		,	8	9	10	activities
				(IRCL	Æ A	NUM	BEK				

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10.5 Appendix 5: Patient Overall Impression of Change

Since the start of the study, my general state of health is: *tick one box only*

[1]	Very Much Improved
[2]	Much Improved
[3]	Minimally Improved
[4]	No Change
[5]	Minimally Worse
[6]	Much Worse

Very Much Worse

[7]

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10.6 Appendix 6: Medication WHO Drug Dictionary Codes

Name	Code
ESA except darbepoetin alfa	ATC level 4 = B03XA [WHODD drug code =
	'00909301001', '00928301001', '07973701001',
	'01703101001']
Darbepoetin alfa	ATC level 4 = B03XA [WHODD drug code =
	'02198701001']
IV Iron	ATC level 4 = B03AC [WHODD drug code =
	'00023501001', '90135401001']
RBC transfusion	ATC level 4 = B05AX [WHODD drug code =
	'01186901001']
Any investigational drug	WHODD drug code = '99999701001'
Hypoxia-inducible factor HIF-PHI	ATC level $4 = B03XA$
Iron-chelating agents	ATC code = $V03AC01$, $V03AC02$ and $V03AC03$
Androgens	ATC level $3 = G03B$ and $G03E$
Dapsone	ATC level 4 = J04BA
Acetaminophen/paracetamol	ATC level 4 = N02BE, N02AA, R05X

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10.7 Appendix 7: Inverse probability censoring weighted model

Background

The possible presence of differential SDD rates between the roxadustat arm and the placebo arm, which may indicate informative censoring, will have a strong impact on the use of conventional survival methodology using Cox regression or other non-parametric survival analysis methods, which may lead to heavy bias in the estimation of the hazard ratio (HR). Patients who dropped out may have dependent or nonrandom censoring. The IPCW approach presented below is often used under these situations.

Step 1: Model the censoring mechanism.

In the censoring model, the event of interest is censoring, hence the subjects who are lost to follow-up have an 'event'. Subjects that are not censored, i.e. those who experience the original event of interest, are now considered censored' since their censoring time is not observed. The probability of being censored will be estimated.

Step 2: Estimate the Product-Limit estimator and Cox proportional hazards estimator

Estimate the P-L estimator and Cox regression estimators using time to censoring for each subject j at each time point t, K $_{j}^{0}$ (t) and K $_{j}^{Z}$ (t). The Cox Model will include e GFR categories (e GFR <=10, 10<= e GFR < 15, 15<= e GFR < 30, and e GFR >= 30), and Dialysis initiation (Yes, No) as time varying covariates. Stratification factors including baseline Hemoglobin values, Study and other common stratification factors will also be included in the model.

Step 3: Calculate the unstablized and stabilized IPCW weights for each of the subjects, j, Wunstab_j (t) =)1/ K_j^z (t), Wstab_j (t) = K_j^0 (t)/ K_j^z (t).

Step 4: Estimate the survival and/or Cox model for time to event in the absence of censoring with the IPCW weights, SIPCW.

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10.8 Appendix 8: Signatures

List of Key Contributors and Approvers

Key Contributors

The following contributed to or reviewed this Statistical Analysis Plan as relevant to their indicated discipline or role.

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Approver Signatories

(E-signatures are attached at end of document)

(E-signatures are attached at end of document)
was the study statistician for this study.
was the Global Statistician Leader and biostatistics peer reviewer of this Statistical Analysis Plan
I approve the contents of this Statistical Analysis Plan:
Astellas Pharma Europe B.V.



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*UTC: Coordinated Universal Time

EXHIBIT C

Statistical Analysis Plan

Study Code D5740C00002

Edition Number 4.0

Date 28 September 2018

A Phase 3, Multicenter, Randomized, Open-Label, Active-Controlled Study of the Safety and Efficacy of Roxadustat in the Treatment of Anemia in Dialysis Patients

A Phase 3, Multicenter, Randomized, Open-Label, Active-Controlled Study of the Safety and Efficacy of Roxadustat in the Treatment of Anemia in Dialysis Patients

Study Statistician

28 Sep 20/8

Date

A Phase 3, Multicenter, Randomized, Open-Label, Active-Controlled Study of the Safety and Efficacy of Roxadustat in the Treatment of Anemia in Dialysis Patients

Global Product Statistician

20)8-09-29

Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate transaminase
ANCOVA	Analysis of Covariance
BIW	Twice weekly
BP	Blood pressure
CHr	Reticulocyte hemoglobin content
CKD	Chronic kidney disease
CKD-DD	Chronic kidney disease with subject on dialysis
CKD-ND	Chronic kidney disease with subject not on dialysis
СМН	Cochran-Mantel-Haenszel
CRF	Case report form
CRP	C-reactive protein
CS	Clinically significant
CSE	Composite safety endpoint
CSP	Clinical study protocol
CSR	Clinical study report
DSMB	Data and safety monitoring board
ECG	Electrocardiogram
ECRF	Electronic case report form
EOS	End of study
EOT	End of treatment
EQ-5D-5L	EuroQol Health Utility Index, 5 dimensions 5 levels
ESA	Erythropoiesis-stimulating agent
FAS	Full Analysis Set
FDA	Food and Drug Administration
Hb	Hemoglobin
HDL	High-density lipoprotein
HR	Hazard ratio
HRQoL	Health Related Quality of Life

Abbreviation or special term	Explanation
ITT	Intention To Treat
IV	Intravenous
KM	Kaplan-Meier
LDL	Low-density lipoprotein
LTFU	Lost to follow up
MACE	Major Adverse Cardiovascular Event
MAP	Mean Arterial Pressure
MAR	Missing At Random
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCMC	Markov Chain Monte Carlo
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model of Repeated Measures
MNAR	Missing Not At Random
N (or n)	Sample size
NCS	Not clinically significant
PCS	Potentially clinically significant
PEY	Patient-exposure-year
PMM	Pattern Mixture Model
PPS	Per-protocol set
PSAP	Pooled Statistical Analysis Plan
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TIBC	Total iron binding capacity
TIW	Three times weekly
TSAT	Transferrin saturation
US	United States
VAS	Visual analogue scale

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Abbreviation or special term	Explanation
WBC	White blood cell

SAP AMENDMENT HISTORY

Date	Brief description of change
28 September 2018	The primary safety objective of this study is to contribute to the safety data in the pool safety analysis. Thus, analyses of CV safety will be conducted in accordance with the pooled safety analysis plan (PSAP) These analyses will be made by study, as described in the PSAP, then pooled adopting meta-analysis techniques.
	The primary efficacy endpoint has been specified as the primary efficacy endpoint for the FDA. The first secondary efficacy endpoint for the FDA has been specified as the primary endpoint for the EU health authorities.
	Another change in this SAP is the ordering of the secondary efficacy endpoints to align with the order of the other phase 3 studies in the DD program.
	The censoring criteria at a primary analysis censoring date has been omitted to align with the censoring rules in the PSAP.
	A full list of the major changes are listed in Section 6.
25 January 2018	The most important change in edition 3.0 is how the analysis of the primary safety composite endpoint MACE is conducted. There has been a strategic change in how to address CV safety in the project. No hypothesis testing, and no formal NI-margin for the safety endpoints will be adopted for this SAP. In alignment with the pooled SAP (PSAP) the focus will be on estimation and in providing a complete and transparent pattern of results for CV safety through the adoption of the "Totality of Evidence" approach. For full details regarding the "Totality of Evidence" approach, please refer to the PSAP.
	Other main changes are the addition of a primary efficacy endpoint, and addition of further secondary endpoints, as well as ordering of the secondary endpoints, done to harmonize with the other pivotal studies in this indication.
	A comprehensive list of changes from the previous edition of the SAP is available in Section 6.

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Date	Brief description of change
08 July 2016	Changes from SAP Edition 1.0: Following comments from the US Food and Drug Administration (FDA) on the CSP on March 13, 2015, it was decided that the analysis method for the first secondary endpoint regarding Hb change to be a multiple imputation ANCOVA. Furthermore, additional changes have been made to align with the CSP amendment, edition 6.0. For all major changes from SAP Edition 1.0, see Section 6.

1. STUDY DETAILS

1.1 Study objectives

This study is part of a study program for chronic kidney disease dialysis dependent (CKD-DD) subjects. The other phase 3 studies in the study program are the FibroGen FG-4592-063 and FG-4592-064 studies and the Astellas 1517-CL-613 study. There is a separate pooled statistical analysis plan (PSAP) for the statistical considerations concerning the overall program. The primary objective of this study is to evaluate the efficacy of roxadustat and to contribute CV safety data to the pooled safety analysis evaluating the safety of roxadustat for the treatment of anemia in CKD subjects on dialysis.

The objectives of the current study are to evaluate the safety and efficacy of roxadustat compared to epoetin alfa for the treatment of anemia in subjects receiving dialysis. Subjects on hemodialysis (HD) or peritoneal dialysis (PD) who have been treated with an erythropoietin analogue or have an indication for treatment with an erythropoietin analogue will be evaluated for eligibility and randomized at a 1:1 ratio to treatment with roxadustat (with discontinuation of prior erythropoietin analogue therapy) or to an active-control group treated with epoetin alfa. This study is also known as "ROCKIES".

1.1.1 Primary efficacy objective

The primary efficacy objective is to evaluate the efficacy of roxadustat as compared to epoetin alfa based on Hb response during the study.

1.1.2 Primary safety objective

The primary safety objective is to contribute adjudicated CV safety data to pooled safety analyses across the phase 3 program per pooled SAP.

1.1.3 Secondary efficacy objectives

The secondary efficacy objectives are to evaluate:

- The efficacy of roxadustat as compared to epoetin alfa based on Hb response and level during the study.
- The efficacy of roxadustat based on Hb response in inflamed subjects.
- The effect of roxadustat on low-density lipoprotein (LDL) cholesterol as compared to epoetin alfa.
- The need for IV iron use in subjects treated with roxadustat as compared to epoetin
- The need for RBC transfusion as rescue therapy in subjects treated with roxadustat as compared to epoetin alfa.

1.1.4 Secondary safety objectives

The secondary safety objective is to evaluate the safety and tolerability of roxadustat as compared to epoetin alfa..

1.2 Study design

This is a Phase 3, multicenter, randomized, open-label, active-controlled study to evaluate the safety and efficacy of roxadustat compared to epoetin alfa for the treatment of anemia in dialysis subjects. Subjects on hemodialysis (HD) or peritoneal dialysis (PD) who have been treated with an erythropoietin analogue or have an indication for treatment with an erythropoietin analogue will be evaluated for eligibility and randomized at a 1:1 ratio to treatment with roxadustat (with discontinuation of prior erythropoietin analogue therapy) or to an active control group treated with epoetin alfa.

The study periods are as follows:

- **Screening Period:** Up to 6 weeks.
- **Treatment Period:** Subjects will be randomized (1:1) to open-label treatment with either roxadustat or epoetin alfa. Treatment duration is variable for individual subjects (estimated treatment up to 4 years). A common closeout will occur when the target number of MACE events has been accrued.
- **Post-Treatment Follow-Up Period:** 4 weeks from the end of treatment (EOT) visit to the end of study (EOS) visit. Subjects who discontinue study medication prematurely will be followed up for CV events, Hb measurements, vital status and hospitalizations until the end of the study (EOS), according to ITT principles, unless consent to participate is withdrawn.

1.2.1 Dosing

Roxadustat

Subjects currently treated with an erythropoietin analogue who are randomized to the roxadustat group will discontinue prior erythropoietin analogue therapy and initiate treatment with roxadustat at a starting dose according to Section 7 in the Clinical Study Protocol (CSP). Moreover, the dose is subsequently adjusted to achieve and maintain Hb levels between 10 and 12 g/dL. Subjects not currently treated with erythropoietin analogue will initiate roxadustat with dose selection based on body weight. Roxadustat will be administered orally three times a week (TIW) throughout the Treatment Period unless dose frequency reduction is required based on Hb levels.

Epoetin alfa

Initial dose selection of epoetin alfa for subjects treated with an erythropoietin analogue will be determined using a conversion table based on the subject's average prescribed

erythropoietin analogue dose during the preceding 4-8 weeks prior to enrollment in the study. Initial dosing of epoetin alfa for subjects not currently receiving an erythropoietin at study entry will be 50 IU/kg TIW with subsequent dose adjustments to achieve an Hb level of 11 g/dL and maintain an Hb level between 10 and 12 g/dL, consistent with approved prescribing information or the Summary of Product Characteristics for epoetin alfa.

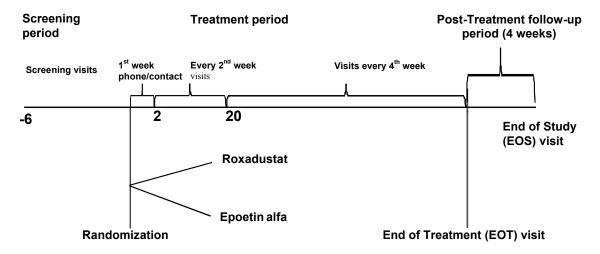
Dosing for both treatment groups

Rescue therapy guidelines are provided to optimize standardization of the use of rescue therapy by investigators and to ensure safety of the individual study subjects. In the event of excessive erythropoiesis or excessive Hb levels equal or greater than 13 g/dL, the dose will be adjusted or put on hold at any time. Excessive erythropoiesis is defined as an Hb increase by >2.0 g/dL within a 4 week period.

1.2.2 Scheduled visits during treatment

During the treatment period, subjects will be contacted by telephone at week 1, and will attend study visits every two weeks from weeks 2 to 20. After week 20, study visits will occur every four weeks until the end of treatment period. A study end date will be defined based on when the planned number of events are estimated to be accrued; the EOT visit will occur as soon as possible after that date. An EOS visit will be performed 4 weeks after the EOT.

Figure 1 Study Flowchart



1.2.3 Stratification variables

The randomization in this study will be stratified by country. The stratification variables for the other studies in the program will be used in the analyses for this study as covariates, with addition of incident vs stable dialysis. The stratification variables are:

- Baseline Hb ($\leq 10.5 \text{ g/dL vs} > 10.5 \text{ g/dL}$)
- 2. cardiovascular/cerebrovascular/thromboembolic medical history (Yes vs. No)
- 3. geographical region (US vs. Ex-US)
- 4. incident vs. stable dialysis (dialysis duration ≤4 months vs >4 months from the randomization date)

Baseline Hb will be included in the analyses as a continuous covariate, hence, not as a dichotomous factor, unless specified otherwise. Throughout this document, the variable cardiovascular/cerebrovascular/thromboembolic medical history will be shortened as CV history, and the variable incident vs stable dialysis will be shortened as dialysis duration

CV history at baseline will be defined for subjects with history of any of the following diseases:

- Myocardial infarction
- Percutaneous coronary intervention
- Coronary artery bypass
- Cardiac failure congestive
- Ischaemic stroke
- Haemorrhagic stroke
- Cerebrovascular accident

1.3 Number of subjects

Primary efficacy variable: With at least 600 subjects, the study will provide at least 99% power to demonstrate non-inferiority of roxadustat versus epoetin alfa for the primary efficacy endpoint (i.e., Hb change from baseline to the average level during the evaluation period defined as Week 28 until Week 52). This assumes a difference (roxadustat minus epoetin alfa) of -0.30 g/dL, a non-inferiority margin for this difference of -0.75 g/dL and a standard deviation of 1.25 g/dL.

To contribute adjudicated CV events for the pooled CV analyses across the phase 3 program: approximately 2000 subjects will be randomized in a 1:1 ratio to either roxadustat or active control, i.e. epoetin alfa. The sample size for this study is driven by the overall requirement of adjudicated CV events for the phase 3 program in dialysis-treated CKD subjects (which consists of four studies in total targeting 611 subjects with MACE events). The three other studies in the study program are FG-4592-064, 1517-CL-0613, FG-4592-063.

, -

2. ANALYSIS SETS

2.1 Definition of analysis sets

2.1.1 Intention To Treat Analysis Set (ITT)

All subjects who have been randomized to study treatment will be included irrespective of their protocol adherence and continued participation in the study. Subjects will be analyzed according to their randomized study medication irrespective of intake of study medication.

2.1.2 Per Protocol Set (PPS)

All randomized subjects without important protocol deviations and who have received at least 8 weeks of study treatment and who have valid corresponding Hb measurements will be included in the PPS. A valid corresponding Hb is defined as an Hb value from the central laboratory that is measured at least 2 weeks after the first dose and was either before the last study drug intake or at maximum three days after the last drug intake. Subjects will be analysed according to their randomized study medication irrespective of intake of study medication. Subjects with an important protocol deviation will be included in the PPS up to the time point when the violation was met. For criteria for PPS exclusion, see Table 1 in Section 2.2. Further details of important protocol deviations are available in a Protocol Deviation Plan. Subjects will be censored at the earliest of date of violating an important protocol deviation, the EOS visit, or at last intake of study drug.

2.1.3 Safety Analysis Set

All subjects who received at least one dose of randomized study drug will be included in the Safety Analysis Set. Throughout the safety results sections, erroneously treated subjects will be accounted for in the actual treatment group. If a subject has received both treatments, only the initial period will be utilized. Subjects will be censored at either, 7, 3 or 0 days after last intake of study drug. Consequently, there will be three versions of the Safety Analysis Set, and they will be referred to as On-treatment+7 (OT+7), OT+3 and OT+0 respectively.

2.1.4 Full Analysis Set (FAS)

The FAS consists of all patients in the ITT analysis set who received at least one dose of study drug and have baseline and at least one post-dose Hb assessment. If actual study medication received differs from the randomized treatment arm, the randomized treatment arm will be used for analysis for the FAS. This analysis set is primarily used for EX-US submissions.

2.1.5 Subjects who will not be included in any analysis sets

Subjects or sites identified prior to database lock (breaking of Sponsor blindness, open-label study) with major Good Clinical Practice violations and where the integrity of the data is strongly questioned through thorough independent investigations will be excluded from all analyses and all analysis sets. This includes but are not limited to subjects who have been identified to be part of a potential fraud investigation, subjects who have not signed an informed consent, subjects randomized in error (e.g. a subject considered to be a screen fail but by mistake randomized in the IWRS due to a technical error). Further, subjects being

randomized more than once will only contribute to the analysis one time. These patients will be analyzed according to their first assigned randomization number and treatment code. All AE's reported for the subjects will be assigned to the subject's first randomization number. All subjects excluded from all analysis sets will be properly documented.

2.2 Violations and deviations

The important protocol deviations are defined in Table 1. Protocol deviations will be presented in a data listing.

Table 1 Criteria for Assessing Important Protocol Deviations

Number	Important Protocol Deviations	Level of Deviation ¹
1	Study drug compliance <75% where drug compliance is measured by comparing dispensed and returned drug (see Section 3.4).	Subject
2	Administration of wrong type of study drug (i.e. the one not randomized to) cumulatively more than 1 week	Visit
3	Administration of prohibited concomitant medication or non-drug therapy as defined in the protocol.	Visit
4	Administration of rescue therapy deviating from the protocol	Visit
6	Violation of inclusion or exclusion criteria. The key inclusion criteria are numbers 3-8. The key exclusion criteria are numbers 1-6, 9-16, 18 and 23. The full inclusion and exclusion criteria is available in the CSP.	Subject

3. PRIMARY AND SECONDARY VARIABLES

3.1 Efficacy variables

3.1.1 Primary efficacy endpoint

US FDA: The primary efficacy endpoint for the US is the mean change from baseline in Hb averaged over week 28 to week 52. A multiple imputation approach with analysis of

Visit-level deviations refer to important protocol deviations that will cause only some data for subjects to be excluded from analyses based on the Per Protocol set, while the subjects remain in the Per Protocol set given that they did not meet any subject-level deviations. Data to be excluded from the Per Protocol analyses could be either data from a certain date, at which the deviation was met for the first time, onwards to the end of the study, or data during a period defined by the start and end dates of the deviation.

¹ Subject-level deviations refer to important protocol deviations that will cause subjects to be excluded from the Per Protocol set, and therefore all their collected data from analyses based on this population.

covariance (ANCOVA) will be applied as a method to handle missing data. Details of the multiple imputation ANCOVA are provided in Sections 4.2.4 and 4.2.5.

Hb results obtained from the central laboratory will be used for all Hb efficacy analyses. Baseline Hb is defined as the mean of the three last central laboratory Hb values from the screening and randomization visits.

Hb values under the influence of a rescue therapy will not be censored.

EU health authorities: The primary efficacy endpoint for the EU health authorities is the mean change from baseline in Hb averaged over week 28 to week 36, without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period.

3.1.2 Hb related secondary efficacy variables

The Hb related secondary efficacy variables are:

- The EU primary endpoint as specified in Section 3.1.1 is the first secondary efficacy endpoint in the analysis for FDA
- Mean change in Hb from baseline to the subjects mean level between week 28 to week 52 in subjects with baseline high-sensitivity C-reactive protein (hsCRP) greater than the Upper Limit Normal (ULN)
- Proportion of total time of Hb ≥10 g/dL from week 28 to week 52. The proportion of total time will be computed as follows: For each subject, the recorded Hb values will first be linearly interpolated between measurements. The time this interpolated curve is ≥10 g/dL will be computed and subsequently divided by the time between the measurements at week 28 and week 52. Subjects without any Hb measurements from week 28 will not be considered for this variable.
- Proportion of total time of Hb within the interval of 10-12 g/dL from week 28 to week 52. The proportion of total time will be computed as follows: For each subject, the recorded Hb values will first be linearly interpolated between measurements. The time this interpolated curve is within 10-12 g/dL will be computed and subsequently divided by the time between the measurement at week 28 and week 52. Patients without any Hb measurements from week 28 will not be considered for this variable.

3.1.3 Lipid related secondary efficacy variables

To evaluate the roxadustat effect on lipids, the following variable will be evaluated

• Mean change from baseline in LDL cholesterol to week 24.

3.1.4 Rescue therapy related secondary efficacy variables

The need for rescue therapy will be evaluated as

• Time-to-first (and proportion of subjects who received) administration of red blood cell (RBC) transfusion as rescue therapy (rescue therapy guidelines are specified in the CSP, Section 7.7.4).

For analyses based on the Safety Analysis set, time to the event will be calculated as the number of days plus one between the day of first dose of study drug and date of the first occurrence of the event, or if no event has occurred before censoring, the date of censoring (see Section 4.1.1). For analyses based on the ITT analysis set, FAS and PPS, time will be calculated as the number of days plus one between the day of randomization and date of the first occurrence of the event, or if no event has occurred before censoring, the date of censoring.

3.1.5 IV iron related secondary efficacy variables

The use of IV iron will be investigated with the variable:

 Average monthly IV iron use per subject during, week 36 to EOS (monthly defined as a period of 4 weeks).

3.1.6 Exploratory variables

The exploratory variables are:

3.1.6.1 Hb related exploratory variables

Mean change from baseline in Hb, utilizing all Hb values from week 28 until the EOT visit. An imputation for mean change in baseline will only be applied for subjects with no Hb values from week 28 to the EOT visit.

- Time to achieving target Hb for anemic (Hb<10 g/dL at baseline) subjects not receiving ESA <= 4 weeks prior to randomization and were ESA-naïve or near ESA-naïve (no ESA use <=4 weeks prior to randomization). Time will be computed analogously as time to first rescue therapy. Target Hb is achieved when Hb level is within 10-12 g/dL at two consecutive measurements. This will be repeated for subjects with no ESA use <= 4 weeks prior to randomization.
- Proportion of ESA-naïve anemic patients achieved Hb response by Week 24 in the subset of patients who were anemic (Hb< 10 g/dL at baseline) and were ESA-naïve or near ESA-naïve (no ESA use <=4 weeks prior to randomization).

Hb response (Yes/No), where Yes is defined as:

○ Hb \geq 11.0 g/dL and Hb increase from baseline by \geq 1.0 g/dL, for subjects with baseline Hb > 8.0 g/dL; or

- o Hb increase from baseline by ≥ 2.0 g/dL, for subjects with baseline Hb ≤ 8.0 g/dL
 - at two consecutive visits [dates] (with available data) separated at least 5 days during the first 24 weeks of treatment without having received rescue therapy (RBC transfusion, ESA, or IV iron) prior to Hb response. The first date of the two consecutive visits will be used as the date of response. The second date of the two consecutive visits will be used when evaluating the presence or absence of rescue therapy.
- Percent of total patient exposure time with achieved Hb level <9, 9-<10, 10-<11, 11 <12, 12-<13, >=13 g/dL during treatment.

3.1.6.2 RBC transfusion related exploratory variables

- Number of rescue therapy treatments given, RBC transfusion per patient exposure year (PEY).
- Proportion of subjects with RBC transfusions during week 28 to week 52.

3.1.6.3 Quality of life related exploratory efficacy variables

European Quality of Life Questionnaire in Five Dimensions, Five Levels (EQ-5D-5L)

The EQ- 5D-5L consists of the EQ-5D-5L descriptive system and the EQ visual analogue scale (VAS). The EQ-5D-5L descriptive system comprises 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, extreme problems. The visual analogue scale records the respondent's self-rated health status on a graduated (0–100) scale, where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state' with higher scores for higher HRQoL. The EQ-5D-5L variables are:

- Change from baseline in EQ-5D-5L index value
- Change from baseline in EQ VAS

and will be computed according to the EQ-5D-5L documentation.

Results from the EQ-5D-5L questionnaire will also be summarized descriptively.

3.1.6.4 Hospitalization related exploratory variables

- Number of hospitalization(s) and number of days of hospitalizations per PEY.
- Number of days spent in Intensive Care Unit (ICU) per PEY.
- Proportion of subjects who are re-admitted to hospital within 30 days per PEY.

- Proportion of subjects who are re-admitted to hospital within 30 days due to heart failure per PEY following a preceding hospitalization due to heart failure.
- Proportion and number of on treatment days of hospitalization-free survival.
- Proportion and number of on treatment days of hospitalization-free, emergency room- free, and skilled nursing facility-free survival. Number of days spent in a Skilled Nursing Facility that follow hospitalizations per PEY, and the total number of days covering both hospitalizations and subsequent days in Skilled Nursing Facility.

3.1.6.5 Other exploratory variables

- Variables concerning serum iron profiles: Iron, TIBC, Ferritin and TSAT. Mean value at each time-point tested, and change from baseline.
- Variables concerning lipids: total cholesterol, high-density lipoprotein (HDL) and triglyceride: mean values and change from baseline at each timepoint tested; percent of subjects who achieved target LDL level <100 mg/dL, at each timepoint; subgroup analyses on patients on statins and those not on statins
- Variables concerning heart rate and blood pressure: heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP).
- Variables concerning concomitant medication: Usage of statins and types of statins, initiation of ESA therapy post study drug discontinuation
- Change from baseline in hepcidin to week 24.

3.2 Safety assessments

Safety will be further assessed by evaluating the following:

- Occurrence of treatment emergent adverse events (TEAEs) and treatment emergent serious adverse events (TESAEs)
- Changes from baseline in vital signs and physical examinations.
- Mean change from baseline in clinical laboratory values.
- Occurrence of clinically significant changes from baseline in vital signs and ECG values.

3.3 Adjudicated CV Events Analyses for Safety Assessments

The CV events being analysed in the PSAP will be adjudicated by the Independent Event Review Committee (IERC) according to the IERC charter. The same adjudication committee will be used for all the phase 3 studies (FG-4592-064, 1517-CL-0613, FG-4592-063, and D5740C00002) in the CKD-NDD program. Analyses of these adjudicated events are described in a separate pooled analysis plan.

3.4 Treatment compliance

Subjects will be asked to return all unused study medication and empty packages to the clinic at each visit. The amount of dispensed and returned study medication will be recorded in the eCRF. The percentage treatment compliance will be calculated as:

((Overall amount of dose actually taken)/(Overall amount of dose to be taken))*100% Subjects taking \geq 75% and \leq 125% of planned study medication are considered to be compliant.

Compliance will be summarized as follows:

- Descriptive statistics will be summarized by the two treatment groups
- Percent compliance will be categorized according to the following three categories:
 - <50% (significant drug non-compliance)</p>
 - \geq 50%, <75%, >125% (moderate drug non-compliance)
 - \geq 75%, \leq 125% (drug compliance)

4. ANALYSIS METHODS

Statistical analyses will be performed by IQVIATM using SAS® Version 9.4 or higher and, where appropriate, additional validated software.

4.1 General principles

All study data will be listed by treatment group, centre, and subject number. Throughout subject data listings, figures and tables, treatment groups will be labelled as "Roxadustat" and "Epoetin alfa".

Study Day will be listed in all data listings whenever an assessment date is presented. Study Day is a relative number, relative to the date of first dose of study drug. Week is also a relative number, relative to the number of weeks from the first dose of study drug. Study Days 1-7 is defined as Week 0, Days 8-14 as Week 1, etc. Clinical events and other variables reported after the EOT visit for a subject will not be included in the primary efficacy and safety

analysis. If collected, these events will be included in tables. Events that are recorded as beginning prior to the date and time of randomization will not be included in a listing.

In addition to specific analyses and presentations that are detailed in the following sections, results will be summarised using descriptive statistics, including the number of subjects (n), mean, standard deviation (SD), median and range (i.e. minimum and maximum) as appropriate. For categorical variables counts and percentage n (%) per treatment group will be presented. Summaries of continuous variables will be based on non-missing observations. For time to event data, the number and percentage of subjects recording the event will be summarised. Ninety-five percent confidence intervals will also be included where appropriate, as a measure of precision. Demographic characteristics, qualifying risk factors and other specific medical and surgical history will be summarised for the ITT analysis set using descriptive statistics. Mean Hb values over time will be graphically displayed and grouped by treatment.

Dates will be presented in the format YYYY-MM-DD.

When the last dose date is missing, it will be imputed as the earliest date of last drug dispense date + number of days of drug dispensed, date of death, date of EOT visit or date of EOS visit.

4.1.1 Censoring

For analyses based on OT+7, subjects will be censored at 7 days after last intake of study drug, or the EOS visit, whichever is earliest.

For analyses based on OT+3, subjects will be censored at 3 days after last intake of study drug, or the EOS visit, whichever is earliest.

For analyses based on OT+0, subjects will be censored at last intake of study drug, or the EOS visit, whichever is earliest.

For analyses based on the ITT analysis set and FAS, subjects will be censored at their individual EOS visit, regardless of if they have discontinued study drug or not. Complete endpoint information will be pursued with every effort for all subjects, unless they exercise their right to withdraw consent. Subjects who withdraw consent will be censored at date of withdrawal of consent, and subjects who are lost to follow up (LTFU) will be censored at last available contact.

Subjects who withdraw consent and for whom only vital status (known to be alive at study closure, or date of death) may be obtained from public records, the occurrence of all components of the primary endpoint cannot be assessed, and will thus be censored at date of consent withdrawn for all analyses. However, the determination of all-cause death will utilize all publicly known mortality data, even that extending beyond date of consent withdrawal. The vital status information will be included in the analysis of all-cause death as a single endpoint, and in sensitivity analysis and tabulations. Similarly, complete information on the endpoint may not be obtained for subjects who are LTFU. Any such subject will be censored in the analysis at the last contact where all elements of the endpoint were assessed. A subject

will not be recorded as LTFU until the end of the study, after every allowable effort to get in contact has been made. Hence, it is anticipated that the number of subjects LTFU will be limited.

4.1.2 Premature permanent discontinuation of study medication

Premature discontinuation from study medication is not the same as withdrawal from the study. As described in Section 3.9 in the CSP there are several options for continuing the study.

It is expected that complete information on the safety composite endpoint events, and as much as possible of the remaining eCRF data, will be obtained for all subjects who prematurely discontinue study medication, unless they refuse any form of follow-up and withdraw consent or are LTFU.

4.1.3 Choice of the non-inferiority margins

Non-inferiority for the Hb efficacy endpoint will be established if the lower limit of the two-sided 95% CI for the difference between the means of the primary endpoint (roxadustat minus control epoetin alfa) is \geq -0.75 g/dL, see Section 0. In other words, a non-inferiority margin of -0.75 g/dL will be used in the Hb efficacy assessments.

Support for the use of a non-inferiority margin of -1.0 g/dL in the peginesatide submission for the dialysis studies was initially provided by estimating the magnitude of the effect of erythropoietin analogue therapy. This estimate was based on summary information from the darbepoetin alfa development program (Aranesp 2001, Omontys 2012), with publicly available summary data. Based on these data, the estimated treatment effect of erythropoietin analogue therapy in the dialysis population was approximately 2.0 g/dL. Based on these data, the estimated treatment effect of erythropoietin analogue therapy in the dialysis population with a 10-12 g/dL target range (at least 2.0 g/dL and was considered to be appreciably larger than 1.0 g/dL, thus supporting the choice of a non-inferiority margin of -1.0 g/dL.

Therefore, the choice of -0.75 g/dL as non-inferiority is more conservative than prior programs, and consequently, an appropriate margin to use.

The comparison between the study drugs for the time-to-first instance of receiving RBC transfusion, or erythropoietin analogue (for roxadustat subjects only) as rescue therapy is also based on a NI evaluation. For this purpose, in the lack of support for the choice from the literature, a 1.8 margin has been selected. NI will thus be claimed if the upper bound of the 2-sided 95% CI for the hazard ratio (roxadustat/epoetin alfa) is less than or equal 1.8.

The analysis of the proportion of total time of Hb within the interval of 11±1 g/dL from week 28 until week 52 between the treatment groups also relies on a non-inferiority evaluation. For this purpose a NI margin of -0.15 has been adopted, i.e. the 2-sided 95% CI around the difference between roxadustat and epoetin alfa has to exceed -0.15. No support from the literature has been found for this selection.

4.2 Analysis methods

4.2.1 Demography

The following will be reported on subjects who are randomised: sex, age, race and ethnic group, baseline Hb value, geographical region, incident vs stable dialysis (dialysis duration ≤4 months vs >4 months from the randomization date), dialysis type, cardiovascular/cerebrovascular/thromboembolic medical history, congestive heart failure history, coronary artery disease history and cerebrovascular history, other relevant medical and surgical history, concomitant medication, weight, height, BMI, tobacco use, CKD diagnosis, diabetes history and baseline blood pressure. Continuous and categorical demographic variables will be presented as described in Section 4.1. The following continuous variables will also be presented as range-based categories:

- baseline Hb value (≤ 10.5 g/dL vs ≥ 10.5 g/dL),
- age $(\ge 18 < 50, \ge 50 < 65, \ge 65 < 75, \ge 75 \text{ years})$,
- BMI ($<30, \ge 30 \text{ kg/m2}$), and
- weight (<70, >=70 <100, >=100 kg).

4.2.2 Confirmatory analysis for the efficacy endpoints

To address the issue of multiple testing while maintaining the overall type-I error, adopting a 5% two-sided significance level, a closed testing sequence will be used for the efficacy endpoints. First, the primary efficacy endpoint analysis according to Section 0 will be performed. If successful, the testing will continue with the secondary efficacy endpoints in the order as specified in Section 4.3.4. Confirmatory statistical hypothesis testing will continue until the first statistically non-significant treatment difference is observed. However, treatment comparisons following and including the first non-significant comparison will be examined in an exploratory manner.

All analyses other than part of this confirmatory analysis will be interpreted descriptively. Consequently, no adjustments for multiplicity will be necessary for such analyses. Ninety-five percent confidence intervals will be calculated, where appropriate, as measures of study precision. P-values may be calculated but are to be regarded as descriptive.

4.2.3 Time to event analysis

For time to event variables, treatments will be compared using a Cox proportional hazards model. Unless specified otherwise baseline Hb as a continuous variable will be used as a covariate, and treatment group, CV history, dialysis duration and geographic region as fixed effects for all analyses. The Efron method will be used for ties. The p-values (calculated using the Wald test), hazard ratio (HR) and 95% confidence intervals for the HR will be reported. Summary tables of these analyses will also include the number of subjects with an event and Kaplan-Meier estimates of the event rates per treatment group estimated at a time point determined on the basis of the available follow-up. Kaplan-Meier estimates of the cumulative proportion of subjects with events will be estimated and plotted, with the number of subjects at risk indicated below the plot at specific time points.

4.2.4 Difference in proportions analysis

For analysis of difference in proportions the approach by Miettinen & Nurminen 1985 will be used and a 2-sided 95% confidence interval for the difference of two proportions (roxadustat vs epoetin alfa) will be computed, adjusting for stratification factors. The model will include the terms of baseline Hb, treatment group, cardiovascular history, geographic region and dialysis duration. The stratified statistics will be based on the standard normal statistic proposed by Gart and Nam 1990.

4.2.5 Analysis of Covariance (ANCOVA)

When using ANCOVA in analysis of change from baseline for a continuous variable, the mean value of all change from baseline values available within the pre-specified timeframe will be used as the dependent variable. Unless specified otherwise, baseline Hb will be used as a covariate and treatment group, cardiovascular history, geographic region and dialysis duration as fixed effects for all analyses. Any further details will be given case-by-case for each endpoint (see Section 4.3). The least squares mean estimates of change from baseline for each treatment group and their difference, and associated 95% CI will be provided.

4.2.6 Multiple imputation ANCOVA

For the primary efficacy analysis, a multiple imputation ANCOVA method (O'Kelly & Ratitch, 2014) will be used. It will be conducted with the following steps:

- 1. 200 datasets will be generated, using seed number 326154, where non-monotone missing Hb data will be imputed, meaning intermediate visits that subjects skip, but return for evaluations at subsequent visits. The data points are imputed assuming MAR, using the MCMC imputation model baseline Hb, CV history, geographic region and dialysis duration, and the available non-missing Hb for each scheduled week are used as covariates, by treatment group. The MCMC statement in the SAS PROC MI procedure with monotone option will be used. As a result, each dataset will only have a monotone missing data pattern.
- 2. For each dataset from step 1, the missing monotone data points will be imputed, which is when a subject misses one visit, and all subsequent visits. As a result, 200 imputed complete datasets will be generated.
 - Missing data at Week 2 will be imputed using the regression imputation model with baseline Hb and Hb from Week 2, CV history, geographic region and dialysis duration as terms in the model, by treatment group This will be performed with the SAS PROC MI procedure with the REGRESSION option in the MONOTONE statement.
 - Repeat for all other scheduled weeks sequentially. Subjects whose missing data were imputed for previous weeks will contribute to the imputation for the current week.
 - The regression imputation model includes an intercept and the slopes of the Hb from previous weeks.

- 3. Fit an ANCOVA model on each of the 200 datasets where the average of the imputed and observed Hb values between weeks 28 to 52 for each subject is taken as the dependent variable and baseline Hb, treatment group, CV history, geographic region and dialysis duration as covariates.
- 4. Combine the results of all 200 ANCOVA models using Rubin's rules (Rubin, 1987) with the SAS PROC MI ANALYZE procedure.

The least squares mean estimates of change from baseline for each treatment group and their difference, together with their associated 95% CI and p-value will be reported.

The exploratory efficacy endpoint of Hb change from baseline to the average between week 28 to the EOT visit will be conducted in the following steps:

- 1. 200 datasets will be generated, using seed number 326154, assuming a return-to-baseline values, with imputed values being sampled from a posterior Bayesian distribution of baseline Hb for all treatment groups combined, using a regression imputation model with stratification variables as predictor variables.
- 2. The imputations will be obtained using SAS PROC MI as follows. The input dataset will contain a set of temporary records to be used for imputation model estimation, where a new record is created for each subject, assigning their baseline Hb value to a variable representing mean Hb values from week 28 to EOT. This variable will be used as a dependent variable in a regression imputation model, thus estimating a distribution of baseline values. The MONOTONE REG statement will be used to estimate the imputation model, and the MNAR statement with MODEL option will be used to specify the subset of temporary records as described above from which the imputation model will be estimated. Once the imputation is complete, the temporary records will be removed prior to analyzing the imputed data, and for subjects whose mean Hb values from week 28 to EOT were imputed, a change from baseline will be calculated as the imputed value minus baseline Hb value.
- 3. Fit an ANCOVA model on each of the resulting 200 datasets where the mean change in Hb from baseline from weeks 28 to EOT for each patient is taken as the dependent variable and baseline Hb, treatment group, CV history, geographic region and dialysis duration as covariates.
- 4. Combine the results of all 200 ANCOVA models using Rubin's rules (Rubin, 1987) with the SAS PROC MIANALYZE.
- 5. Non-inferiority between roxadustat compared to epoetin alfa will be declared, and this test successful, if the lower bound of the 2-sided 95% confidence interval of the difference between roxadustat and epoetin alfa exceeds -0.75 g/dL.

4.2.7 Mixed Model of Repeated Measures (MMRM)

As one of the sensitivity analyses, the mixed model of repeated measures (MMRM) will be used. Longitudinal models with correlated errors, otherwise widely known as MMRMs, have been increasingly used for the analysis of clinical trials with missing data. A longitudinal model is often used even though the primary objective is to estimate a treatment effect and test a null hypothesis of no treatment effect at a single specific time-point (typically at the end of double-blind period). The advantage of using an MMRM analysis in this context (compared to ANCOVA at the primary time-point) is that longitudinal models include all randomized subjects regardless of whether they completed the study (provided data for the primary time-point) or not. Model estimation and inference is done without performing any imputation of the missing data for subjects who discontinued early, yet partial data available for these subjects is fully utilized and contributes to the estimation of effects and to the variance-covariance structure of the longitudinal model.

The MMRM can contain terms for baseline measurement, treatment arm, visit, treatment by visit interaction, and the stratification variables. Details will be given case-by-case for each endpoint. The least squares mean estimates of change from baseline for each treatment group and their difference, and associated 95% CI will be provided. Due to the large amount of visits to include in the model, the unstructured covariance pattern model will be selected first. If the algorithm for unstructured covariance pattern does not converge, then the heterogeneous Toeplitz structure will be used instead. If this second model also does not converge, then the (homogeneous) Toeplitz structure will be selected, thereafter the compound symmetry and finally the first order autoregressive covariance structure will be used to achieve convergence.

4.2.8 Pattern Mixture Models

To address the possibility of the Hb data being missing not at random (MNAR), Pattern Mixture Models (PMM) will be implemented as sensitivity analyses. Pattern Mixture Models (PMM) provide a general and flexible framework for sensitivity analyses that allows formulating assumptions regarding missing data in a transparent and clinically interpretable manner. A variety of PMMs with different types of MNAR assumptions will be implemented.

4.2.8.1 PMM -Last Mean Carried Forward

A pattern-mixture model using a last mean carried forward multiple imputation method (Carpenter et al, 2013) will be used as another sensitivity analysis to explore the robustness of the ANCOVA results for the primary efficacy variables. Using this method, missing data after ending Week will be imputed based on the last non-missing mean from its own treatment group.

The steps to implement this sensitivity method is the same as for the multiple imputation ANCOVA method described in Section 4.2.6 with the exception of step 2, where the monotone datasets are imputed. The procedure for that is as follows. Parameters below refer to the parameters of the multivariate normal distribution for baseline and post baseline Hb measurement.

- 1. Create posterior distribution of parameters: Separately for each treatment group, take all subjects observed data and assuming MAR to fit a multivariate normal distribution with unstructured mean (i.e. a separate mean for each of the baseline plus post-baseline scheduled weeks and unstructured variance covariance matrix using a Bayesian approach with an improper prior for the mean and an uninformative Jereys' prior for the variance-covariance matrix (Schafer, 1997, p. 155).
- 2. Draw parameters: Separately for each treatment group, draw variance-covariance matrix from the posterior distribution for the parameters using seed 453628. The mean Vector would be set to the marginal mean for their randomized treatment arm at their last non-missing measurement.
- 3. Build joint distribution of missing data and observed data: For each subject with missing data, using the draws for the parameter to build the joint distribution of their observed and missing data.
- 4. Construct conditional distribution of missing data give observed data: For each subject with missing data, use their joint distribution in previous step to construct their conditional distribution of missing given observed outcome data. Sample their missing data from this conditional distribution, to create a "completed" data set, using seed 732545.

Repeat the above steps for 200 times and resulting in 200 fully imputed data sets. Then fit an ANCOVA model for each imputation data set, and combine the resulting parameter estimates and standard errors using Rubin's rules (Rubin, 1987) for final inference.

4.2.8.2 PMM –Baseline Carried Forward (roxadustat only and both groups)

The analysis is similar to PMM – Last Mean Carried Forward, with a different assumption in imputing the missing data. The imputation data will be generated similarly as last mean carried forward method described above but instead of using post-baseline observed data, only baseline data will be used. The similar analyses will be conducted in two scenarios.

- The baseline carried forward imputation will be performed for the roxadustat treatment group only, while for active control group, the imputation data will be generated using the last mean carried forward described above.
- The baseline carried forward imputation will be performed for both treatment groups.

Similarly, the Rubin's method will be then used to combine the estimates and the differences between the least square mean differences between the two treatment groups from each of the ANCOVA analysis.

4.3 Statistical Analyses

4.3.1 CV safety endpoints analyses

The CV safety evaluation strategy is to conduct pooled analyses of adjudicated data across the study program to ensure that the overall number of events is high enough to provide adequate power. Thus, all analyses of CV safety will be conducted in accordance with the PSAP.

4.3.2 Primary efficacy endpoint analysis for US

Mean change in Hb from baseline to the subjects mean level from week 28 to week 52 will analyzed with multiple imputation ANCOVA as described in Section 4.2.5 and 4.2.6. The model will contain terms for the baseline Hb measurement, treatment arm, CV history, geographic region and dialysis duration. Non-inferiority of roxadustat compared to epoetin alfa will be declared, and this test as successful, if the lower bound of the 2-sided 95% confidence interval of the difference between roxadustat and epoetin alfa exceeds -0.75 g/dL. The ITT analysis set will be used.

4.3.3 Primary efficacy endpoint analysis for EU (First Secondary endpoint for FDA)

Mean change in Hb from baseline to the subjects mean level from week 28 to week 36, without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period and will be analysed using MMRM. The model will contain terms for the baseline Hb measurement, treatment arm, visit, visit by treatment, CV history, geographic region and dialysis duration. Data up to visit of Week 52 will be included in the model.

Non-inferiority of roxadustat compared to epoetin alfa will be declared, and this test as successful, if the lower bound of the 2-sided 95% confidence interval of the difference between roxadustat and epoetin alfa exceeds -0.75 g/dL. The PPS will be used for non-inferiority. In addition to the comparison based on the PPS population, to address the formal test for non-inferiority, results will also be provided based on the FAS population, to allow also for a potential superiority comparison. The latter test is not part of the formal testing sequence.

4.3.4 Secondary efficacy endpoints analyses

Secondary efficacy endpoints will be tested using a fixed sequence approach to adjust for multiple testing. If the p-value from a test is less than 0.05, the test will be declared as successful and the analysis will continue to the next comparison in the sequence. Formal statistical hypothesis testing will be stopped as soon as a test is accompanied by a p-value ≥ 0.05 . The PPS will be used for the first secondary endpoint for non-inferiority, OT+3 analysis set will be used for the secondary endpoints related to RBC transfusion as rescue therapy, and the ITT analysis data set will be used for all the remaining secondary endpoints.

1. The EU primary endpoint for non-inferiority is the first secondary efficacy endpoint for FDA (see above).

- 2. Mean change from baseline in LDL cholesterol to week 24 will be analysed using ANCOVA. Baseline Hb and baseline LDL will be used as covariates and treatment groups, CV history, geographic region and dialysis duration as fixed effects. Superiority will be declared if the upper bound of the 2-sided 95% confidence interval of the difference between roxadustat and epoetin alfa falls below 0.
- 3. Mean change in Hb from baseline to the subjects mean level from week 28 to week 52 in subjects with baseline hsCRP greater than the Upper Limit Normal (ULN) will be analysed analogously as the primary efficacy endpoint. Superiority of roxadustat compared to epoetin alfa will be declared, and this test as successful, if the lower bound of the 2-sided 95% confidence interval of the difference between roxadustat and epoetin alfa exceeds 0 g/dL.
- 4. Proportion of total time of interpolated Hb values ≥ 10 g/dL from week 28 until week 52 will be estimated for each subject and used as dependent variable. The difference between roxadustat and epoetin alfa will be compared using ANCOVA. Baseline Hb will be used as a covariate and the treatment groups, CV history, geographic region and dialysis duration as fixed effects. Non-inferiority between the groups will be declared, and this test as successful, if the lower bound of the 2-sided 95% confidence interval of the difference between roxadustat and epoetin alfa exceeds -0.15.
- 5. Proportion of total time of interpolated Hb values within the interval 10-12 g/dL from week 28 until week 52 will be estimated for each subject and used as dependent variable. The difference between roxadustat and epoetin alfa will be compared using ANCOVA. Baseline Hb will be used as a covariate and the treatment groups, CV history, geographic region and dialysis duration as fixed effects. Non-inferiority between the groups will be declared, and this test as successful, if the lower bound of the 2-sided 95% confidence interval of the difference between roxadustat and epoetin alfa exceeds -0.15.
- 6. The average monthly IV iron use during Week 36 to EOS will be compared between the two treatment groups using a Wilcoxon Rank Sum test. Superiority will be declared if the p-value is less than 0.05.
- 7. Time-to-first (and proportion of subjects who received) RBC transfusion as rescue therapy, will be analysed using Cox proportional hazard model. The baseline Hb, geographic region, dialysis duration and CV history will be included as covariates. Non-inferiority will be claimed, and this test successful, if the upper bound of the 2-sided 95% CI for the hazard ratio (roxadustat/epoetin alfa) is less than or equal to 1.8.

4.3.5 Exploratory endpoint analysis

The baseline value for each exploratory variable is defined as the last measurement of the variable prior to randomization, including the measurement from the randomization visit, unless stated otherwise.

The analysis set to be used for all exploratory analyses will be ITT analysis set, unless specified otherwise. The variables will be analysed as follows:

4.3.5.1 Hb related exploratory endpoint analysis

- Mean change from baseline in Hb to the subjects mean level from week 28 to EOT will be analyzed using multiple imputation with ANCOVA as described in Section 4.2.6. The mean change from baseline will only be imputed for subjects with no measurements from week 28 to EOT. Non-inferiority of roxadustat compared to epoetin alfa will be declared, and this test as successful, if the lower bound of the 2-sided 95% confidence interval of the difference between roxadustat and epoetin alfa exceeds -0.75 g/dL.
- Mean change in Hb from baseline to the subjects mean level from week 28 to week 36 in subjects with baseline hsCRP greater than the Upper Limit Normal (ULN) will be analysed analogously as the primary efficacy endpoint. PPS will be used.
- Proportion of total time of interpolated Hb values ≥10 g/dL from week 28 until week 36 will be estimated for each subject and used as dependent variable. The difference between roxadustat and epoetin alfa will be compared using ANCOVA with treatment group, geographic region and CV history as fixed factors and baseline Hb and baseline eGFR as covariates. PPS will be used.
- Time to achieving target Hb for anemic (Hb<10 g/dL at baseline) subjects who were ESA-naïve or near ESA-naïve (no ESA use <=4 weeks prior to randomization). This will be analyzed analogously as Time to first rescue therapy (composite). Target Hb is achieved when Hb level is within 10-12 g/dL at two consecutive measurements.
- Estimation of median time (in weeks) to achieve target Hb for anemic (Hb<10 g/dL who were ESA-naïve or near ESA-naïve (no ESA use <=4 weeks prior to randomization), based on the definition of two consecutive Hb levels within 10-12 g/dl, by treatment arm.
- Proportion of ESA-naïve anemic patients achieved Hb response by Week 24 in the subset of patients who were anemic (Hb< 10 g/dL at baseline) and were ESA-naïve or near ESA-naïve (no ESA use <=4 weeks prior to randomization).

Hb response (Yes/No), where Yes is defined as:

- Hb \geq 11.0 g/dL and Hb increase from baseline by \geq 1.0 g/dL, for subjects with baseline Hb > 8.0 g/dL; or
- Hb increase from baseline by ≥ 2.0 g/dL, for subjects with baseline Hb ≤ 8.0 g/dL
 - at two consecutive visits [dates] (with available data) separated at least 5 days during the first 24 weeks of treatment without having received rescue therapy

(RBC transfusion, ESA, or IV iron) prior to Hb response. The proportion of responders in the primary efficacy variable will be compared using Miettinen & Nurminen model, adjusting for the region, history of CV, baseline Hb (<=8, >8 g/dL) and dialysis duration, comparing roxadustat to epoetin alfa.

4.3.5.2 Rescue therapy related exploratory endpoint analysis

- Time-to-first instance rescue therapy (composite) of receiving RBC transfusions, or erythropoietin analogue as rescue therapy will be analysed analogously as Time to first RBC transfusion in Section 4.3.4. The OT+3 will be used.
- Number of rescue therapy treatments given; RBC transfusion or erythropoietin analogue per PEY will be reported descriptively, together and separately. The OT+3 will be used.
- Proportion of subjects receiving RBC transfusion during week 28 to week 52 will be analysed using Miettinen & Nurminen model adjusting for the region, history of CV and baseline Hb (<=8, >8 g/dL) and dialysis duration, comparing roxadustat to epoetin alfa. The OT+3 will be used.

4.3.5.3 Quality of life related exploratory endpoint analysis

- Mean change in EQ-5D-5L index value from baseline to average EQ-5D-5L index value of weeks 28-52 will be analyzed using MMRM with treatment, visit, treatment-by-visit interaction, and baseline covariates, including the baseline index value, baseline Hb, CV history, geographic region and dialysis duration, as fixed effects and subject as a random effect.
- Change in EQ-5D-5L index value from baseline at weeks 12, 28 and 52 will be analyzed using the same MMRM as specified in Section 4.3.4 for this variable.
- Shift tables of EQ-5D-5L levels 1-5 by dimension and treatment arm.
- Mean change in EQ-5D-5L VAS value from baseline to average EQ-5D-5L VAS value of weeks 28-52 will be analyzed using MMRM with treatment, visit, treatment-by-visit interaction, and baseline covariates, including the baseline VAS value, baseline Hb, CV history, geographic region and dialysis duration, as fixed effects and subject as a random effect.
- Change in EQ-5D-5L VAS value from baseline at weeks 12, 28 and 52 will be analyzed using the same MMRM as specified above for this variable.
- EQ index value and VAS mean values (+SD) and median values (+25th & 75th percentiles) at baseline and each visit per treatment arm.

4.3.5.4 Hospitalization related exploratory endpoint analysis

All endpoints in this subsection will use OT+7.

- Proportion of subjects with hospitalizations and number of days of hospitalizations per PEY will be reported descriptively.
- Number of days spent in ICU per PEY for each treatment arm will be reported descriptively.
- Proportion of subjects who are re-admitted to hospital within 30 days per patientexposure year for each arm will be reported descriptively.
- Proportion of subjects who are re-admitted to hospital within 30 days due to heart failure preceding a hospitalization due to heart failure per PEY for each arm will be reported descriptively.
- Proportion of subjects by number of days spent in a Skilled Nursing Facility that follow hospitalizations per PEY will be reported descriptively.
- Proportion and number of days of hospitalization-free survival on treatment will be reported descriptively.
- Proportion and number of days of hospitalization-free, emergency room- free, and skilled nursing facility-free survival on treatment will be reported descriptively. Proportion of subjects with days spent in a Skilled Nursing Facility that follow hospitalization and number of days spent in a Skilled Nursing Facility that follow hospitalizations per PEY will be reported descriptively. The total number of days covering both hospitalizations and subsequent days in Skilled Nursing Facility will also be reported.

4.3.5.5 Other exploratory endpoint analysis

- The average monthly IV iron use during Week 0 to 36 and week 28 to 36 will be compared between the two treatment groups analogously as the secondary efficacy endpoint of IV iron.
- Average monthly IV iron usage per PEY per arm will be reported descriptively.
- Mean change in heart rate from baseline throughout week 28 to the EOT visit. For each subject, the change from baseline to the mean level across all heart rate values from week 28 until the EOT visit will be used as the dependent variable. An ANCOVA approach will be used with baseline heart rate, baseline Hb as covariates and the treatment groups, CV history, geographic region and dialysis duration as fixed effects.

- Change in blood pressure (DBP, SBP and MAP) from baseline throughout week 28 to the EOT visit. Analysis will be conducted using ANCOVA analogously as the analysis of change in heart rate.
- Iron parameters: Serum iron, TIBC, Ferritin and TSAT level at each testing timepoint and mean change from baseline throughout week 28 to the EOT visit. For each of the serum profiles, analysis will be conducted using ANCOVA analogously as the analysis of change in heart rate.
- Change in variables concerning lipids: Total cholesterol, LDL, HDL and triglyceride. For each of the lipids, analysis will be conducted using ANCOVA analogously as the analysis of change in heart rate, from week 24 to the EOT visit. Percent of subjects who achieved target LDL level <100 mg/dL will also be compared at all available time points
- The usage of statins, types of statins and statin dose levels will be reported descriptively.
- Subject initiation of ESA therapy post study drug discontinuation will be reported descriptively.
- Change from baseline in hepcidin to week 24. Analysis will be conducted using ANCOVA analogously as the analysis of change in heart rate.

4.3.6 Sensitivity analysis of efficacy endpoints

- The analysis of the primary efficacy endpoint for US will be repeated but will exclude Hb values 6 weeks after the use of rescue therapy. ITT analysis set will be used.
- The analyses of primary efficacy endpoint and the secondary efficacy endpoints will be repeated using the OT+7.
- The analysis of the US primary efficacy endpoint and the Hb related secondary efficacy endpoints will be repeated using the PPS.
- The secondary endpoint of RBC transfusion as rescue therapy will be repeated using the ITT analysis set.
- Change in Hb from baseline using MMRM. Mean change from baseline across all Hb values from week 28 to week 52 will be analysed using baseline Hb as a covariate and treatment group, visit, visit by treatment interaction, CV history, geographic region and dialysis duration as fixed effects. ITT analysis set will be used.

- Proportion of total time of interpolated Hb within the interval of 10-12 g/dL from week 28 to the EOT visit. The difference between roxadustat and epoetin alfa will be compared using an ANCOVA model with baseline Hb as a covariate, and CV history, geographic region and dialysis duration, as fixed effects. ITT analysis set will be used.
- Change in Hb from baseline using PMM Last Mean Carried Forward, as specified in Section 4.2.8.1. ITT analysis set will be used.
- Change in Hb from baseline using PMM PMM Baseline Mean Carried Forward (ANCOVA), as specified in Section 4.2.8.2. ITT analysis set will be used.
- Change in Hb from baseline using PMM Baseline Mean Carried Forward for roxadustat subjects, MAR assumption for epoetin alfa group (ANCOVA), as specified in Section 4.2.8.2. ITT analysis set will be used.

4.3.7 Subgroup analyses

Subgroup analysis will be performed for both the primary efficacy endpoints of Hb, with the ITT analysis set for the primary endpoint for US and the PPS for the primary endpoint for EU.

- Age: <65 and ≥ 65 ; <75 and ≥ 75 years
- Gender: Male vs Female
- Race: White, Black or African American, Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaska native, other
- Weight: $<70 \text{ kg vs} \ge 70 \text{ kg}$; and $<100 \text{ kg vs} \ge 100 \text{ kg}$
- Weight by gender-specific median (4 groups)
- Body mass index (BMI): <30 and $\ge 30 \text{ kg/m}^2$
- Geographical region: US vs Ex-US
- Geographical region:
 - North America
 - South America
 - Asia and Australia
 - Europe
- Peritoneal dialysis vs. Hemodialysis

- Cardiovascular/cerebrovascular/thromboembolic history: Yes or No
- Baseline Hb value: ≤ 10.5 g/dL and ≥ 10.5 g/dL
- Incident vs stable dialysis: dialysis duration ≤4 months vs >4 months from the randomization date
- Diabetes history: Yes vs No
- Epoetin alfa dose prior to randomization: ≤ 12,500 IU/week and >12,500 IU/week
- Baseline hsCRP (≤ULN vs >ULN).

4.3.8 Safety assessment analysis

The safety analysis will be performed using the OT+7. Safety variables include adverse events (AE), laboratory variables, vital signs, ECG variables and physical examinations. For each safety variable, the last assessment made on the screening visits or the randomization visit will be used as the baseline for all analyses, unless specified otherwise.

4.3.8.1 Adverse events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 higher.

An AE (classified by preferred term) started during the treatment period will be considered a treatment-emergent adverse event (TEAE) if it was not present prior to the first dose of study medication. An AE that starts more than 7 days after the last dose of study medication will not be counted as a TEAE.

The number, percentage and percentage per PEY of subjects reporting TEAEs in each treatment group will be tabulated by system organ class and preferred term; by system organ class; by preferred term and by system organ class, preferred term, and relationship to study medication. If more than one event occurs with the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the study medication. In addition to reporting TEAEs by number of subjects, the table by system organ class and preferred term will also be reported by patient years and event rates. Thus, allowing for potential systematic differences in mean exposure between the treatment groups. The event rate for a particular AE will be derived as the number of subjects with the AE, divided by total number of days at risk for the AE across all subjects in given group, multiplied by 365.25 multiplied by 100.

The distribution of TEAEs by severity and relationship to study medication will be summarized by treatment group.

The incidence of common (≥5% of subjects in any treatment group) TEAEs, common treatment-emergent serious AEs (TESAE), and AEs leading to discontinuation of study medication will be summarized by preferred term and treatment group, sorted in decreasing overall (across treatments) frequency. Moreover, TEAEs leading to hospitalization by system organ class and preferred term will be presented. In addition, related deaths and fatal SAEs (i.e., events that caused death) will be summarized separately by treatment group, system organ class and preferred term. TEAEs with outcome of deaths and TESAEs will also be presented for the ITT analysis set.

TEAEs and TESAEs by system organ class and preferred term will also be reported with OT+3 and OT+0.

Listings will be presented of subjects with serious adverse events (SAEs), subjects with adverse events leading to discontinuation, and subjects who died.

4.3.8.2 Laboratory variables

Descriptive statistics for laboratory values and mean percent changes from baseline at each assessment time point will be presented by treatment group for the following laboratory variables collected in the study:

- Hematology: Hemoglobin, hematocrit, RBC count, MCV, MCH, MCHC, WBC count, WBC differential, platelet counts and Reticulocyte count
- Chemistry: Alkaline phosphatase, ALT, AST, total bilirubin, LDH, total protein, albumin, fasting glucose, phosphate, uric acid, BUN, creatinine, sodium, and potassium.
- Serum iron, ferritin, TIBC, TSAT
- CHr
- Hepcidin and hsCRP

The laboratory values will be presented in SI units, except for Hb, ALT, AST, ALP and Gamma Glutamyl Transferase, which will be presented in conventional units

4.3.8.3 Vital signs

Blood pressure baselines are defined as the average of all measurements from the screening visits and randomization visit. For subjects on hemodialysis, vital signs should be recorded pre-dialysis. For subjects on peritoneal dialysis, vital signs may be recorded at any time during the visit

Descriptive statistics for vital signs (e.g., systolic and diastolic blood pressure and MAP) and their changes from baseline at each visit and at the end of study will be presented by treatment group.

Vital sign values are potentially clinically significant (PCS) if they meet both the observed value criteria and the change from baseline criteria listed in Table 2 below. The number and percentage of subjects with post-baseline PCS values will be tabulated by treatment group.

Table 2 Criteria for Potentially Clinically Significant Vital Signs

Vital Sign Parameter	Flag	Criteria*	
		Observed Value	Change
Systolic Blood Pressure	High	≥170	Increase of ≥20
(mmHg)	Low	≤90	Decrease of ≥20
Diastolic Blood	High	≥110	Increase of ≥15
Pressure (mmHg)	Low	≤45	Decrease of ≥15
Pulse Rate (bpm)	High	≥120	Increase of ≥20
	Low	≤50	Decrease of ≥20

^{*} A post-baseline pre-dialysis or post-dialysis value is considered as a PCS value if it meets both criteria for observed value and change from pre-dialysis or post-dialysis baseline

4.3.8.4 Electrocardiogram

QTc interval will be calculated using both Bazett (QTcB = QT/(RR) $^{1/2}$) and Fridericia (QTcF = QT/(RR) $^{1/3}$) corrections; and if RR is not available, it will be replaced with 60/HR in the correction formula.

Box plots for each variable versus visit will be produced by treatment group (roxadustat vs. epoetin alfa).

ECG values are PCS if they meet or exceed the upper limit values listed in Table 3 below. The number and percentage of subjects with post-baseline PCS values will be tabulated by treatment group. The percentages are to be calculated relative to the number of subjects with available baseline and at least one post-baseline assessment. The numerator is the total number of subjects with at least one post-baseline PCS ECG value.

 Table 3
 Criteria for Potentially Clinically Significant ECG

ECG Parameter	Unit	High Limit
QRS interval	Msec	≥150
PR interval	Msec	≥250
QTc interval	Msec	>500; Change from baseline >30 and >60

4.3.8.5 Physical examination

Incidence of physical examination abnormalities will be summarized for the randomization visit and the EOT visit by treatment group. Shift tables of baseline vs last observation will be provided.

4.3.9 Population PK analysis

A population PK analysis of data collected in the CKD-dialysis dependent program will be performed as outlined in a separate population PK analysis plan.

5. INTERIM ANALYSES

No interim analysis specific to this study will be conducted.

6. CHANGES OF ANALYSIS FROM PROTOCOL

There are no changes of analysis from protocol version 8.0, 19 September 2018.

6.1 Changes of analysis from previous edition of the SAP

Table 4 Major changes of analysis from SAP Edition 3.0

SAP Section	Description of change	Rationale
1.1	The objectives of the study have been split to efficacy objectives and safety objectives.	For clarification.
1.1.4	A secondary objective to evaluate the efficacy of roxadustat based on Hb response in inflamed subjects has been added	To harmonize with the secondary objectives of the other phase III studies in the program.
	A secondary objective to evaluate the effect of roxadustat on LDL cholesterol has been added.	
	The secondary objective of the effect on self-reported health status has been removed.	
1.3	The description of the determination of the sample size related to CV safety has been shortened	Reference to a more detailed description of the requirements for sample size to address CV safety for this

		indication is made to the pooled statistical analysis plan.
2.1.1	FAS is renamed as ITT analysis set.	To align with the definition and terminology adopted in the other phase 3 trials in the study program.
2.1.2	An additional criteria to PPS has been added, which requires subjects to be on study drug for at least 8 weeks.	To align with the definitions adopted in the other phase 3 trials in the study program, and for clarification.
2.1.3	Added additional safety analysis sets; OT+7, OT+3 and OT+0. Removed OT+28.	To align with safety analysis sets in the PSAP.
	Full analysis set (FAS) is newly defined in a new section, Section 2.1.4.	To align with the definitions and terminology adopted in the other phase 3 trials in the study program, this analysis set will be required for the EU submission.
	Have added a subsection 2.1.5 that describes how subjects who will not be included in any analysis sets will be handled.	Not included in previous editions of the SAP.
2.2	Changed the level of deviation for the important protocol deviation of compliance to subject level from visit level.	To simplify the derivation of compliance and harmonize with the other phase III studies in the program
3	The structure of this section and its subsections are rearranged. The subsection on primary efficacy variables is split into two parts, one for US FDA and the other for EU health authority. The subsections on primary and	To harmonize with the primary variables of the other phase III studies in the program
	secondary safety variables is renamed as "Adjudicated CV events Analyses	

	for Safety Assessments" and its description is replaced by new texts on the pooling of the adjudicated composite safety endpoints from all the phase 3 studies of the program.	
Subsections of Section 3 related to secondary and exploratory efficacy variables	The primary efficacy variable designated for EU health authority is added as the first Hb-related secondary efficacy variable designated for US FDA.	To harmonize with the secondary variables of the other phase III studies in the program
	Changed the timing of the hsCRP variable to the average level between week 28 to week 52.	
	Added a variable for proportion of total time of interpolated Hb values ≥10 g/dL from week 28 until week 52 to the secondary variables. A corresponding analysis has been added to Section 4 as a secondary efficacy analysis.	
	Downgraded the secondary variables of mean change from baseline in Hb, averaged over week 28 to EOT visit, Hb response, FACT-An variable, PGIC variable and EQ-5D-5L variable to exploratory variables and their corresponding analyses to exploratory in Section 4.	
	Added a new section for lipid related secondary efficacy variables. A corresponding analysis has been added as a secondary efficacy analysis in Section 4.	To investigate the added secondary objective to evaluate LDL cholesterol.
	Added exploratory endpoint of proportion of subjects with RBC transfusion within weeks 28-52 in	

	Section 3 and the corresponding exploratory analysis in Section 4.	Exploratory variables and analyses of interest
	Added exploratory endpoint of proportion of anemic ESA-naïve subjects in Section 3 and the corresponding exploratory analysis in Section 4.	
	Added exploratory variables related to hospitalization-free, emergency roomfree, and skilled nursing facility-free survival in Section 3 and their corresponding exploratory analysis in Section 4.	
	Added exploratory variables for measuring the proportion of time subjects were on different Hb levels in Section 3 and their corresponding exploratory analysis in Section 4.	
	Added exploratory variables that repeat the secondary endpoints number 3, 4 and 6 on the time period week 28 to week 36.	
3.4	Changed the derivation of compliance	To harmonize with the definition with the other phase 3 studies in the program
4.1	A method to impute the last dose date, if missing, has been added.	To handle missing last dose dates.
4.1.1	The criteria to censor at PACD has been removed.	To harmonize with the censoring rules of the PSAP.
	Subjects will be censored at the EOS instead of EOT for FAS.	
4.1.4	Deleted Section "Investigation of informative censoring".	Not applicable since the CV analyses will not be performed for the individual CSR.

4.2.6	Decreased the number of multiple imputations to 200 from 1000.	To reduce the computational runtime.	
Subsections of Section 4 related to statistical analyses on CV	Removed the statistical analyses of the adjudicated CV events from this SAP.	All analyses of CV safety will be conducted in accordance with the PSAP, and will not be done for the individual CSR.	
Safety	Deleted section "Model checking".		
		Not applicable since the CV analyses will not be performed for the individual CSR.	
Subsections of Section 4 related to statistical analysis on	The section on primary efficacy endpoint analysis is split into two sections, one for US FDA and the other for EU health authority.	To harmonize with the primary variables of the other phase III studies in the program	
efficacy	The primary efficacy endpoint designated for EU health authority is added as the first secondary efficacy endpoint designated for US FDA Changed the ordering of the secondary efficacy endpoints. The PPS will be used for the first secondary endpoint, OT+3 analysis set will be used for the secondary endpoints related to RBC transfusion as rescue therapy, and the ITT analysis data set will be used for all the remaining secondary endpoints. Changed the analysis model of IV iron to Wilcoxon Rank Sum test.	To harmonize with the secondary endpoints of the other phase III studies in the program. A decision based on balancing clinical importance of different endpoints together with the likelihood for success. To better the fit the distribution of the IV iron data.	
	Analyses of the exploratory efficacy endpoints newly added in Section 3 are specified accordingly.	Analyses of interest	

	The analysis data sets of individual sensitivity analyses are updated, and new sensitivity analyses are added.	To harmonize with the sensitivity analyses of the other phase III studies in the program
4.3.10.1	The sentence "Finally, TESAEs that occurred during the 4-week period preceding an excessive erythropoiesis event will be presented by system organ class, preferred term and treatment group" is removed. Change the safety analyses to be on OT+7 instead of OT+28.	To align with safety analysis sets in the PSAP and the safety analysis in the other phase 3 studies in the program.
	Added analyses on key safety variables for OT+7, OT+3 and OT+0.	Analyses of interest.
4.3.10.3	Vital sign baseline definition has changed from using the last assessment prior to the first dose to the average of all measurements from the screening visits and randomization visit.	Deemed to be a more meaningful definition of the baseline from a clinical perspective.

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8. APPENDIX

Not applicable.

EXHIBIT D

NCT # NCT02052310

FibroGen, Inc.

Protocol Number: FGCL-4592-063

A Phase 3, Multicenter, Randomized, Open-Label, Active-Controlled Study of the Efficacy and Safety of Roxadustat in the Treatment of Anemia in Incident Dialysis Patients

Protocol Amendment 4

STATISTICAL ANALYSIS PLAN

Version: V1.0

Release Date: 14Oct2018

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FGCL-4592-063

Statistical Analysis Plan, v1.0

11/23/2020

Approvals

I have reviewed and accept the information in this document to be a true and accurate representation of the Statistical Analysis Plan for Study FGCL-4592-063.

Initiator: Signature: Date: Reviewed by: Signature: Date: Signature: Date: Signature: Date: Signature: Date: Signature: Date:

Signature Significance

The following significance is lent to the signatures on the *Approvals* page of this document.

FGCL-4592-063

Statistical Analysis Plan, v1.0

11/23/2020

Signature	Significance
Author	By signing, the author is attesting that the content of the document is complete and accurate.
Reviewer	By signing, the reviewer is attesting that the document's approach and contents are compliant with the study protocol, all appropriate, regulatory requirements, and other significant guidelines. This individual(s) has reviewed the document for accuracy and completeness.

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LIST OF ABBREVIATIONS

AE Adverse Event

ANCOVA Analysis of Covariance

ANOVA Analysis of Variance

ATC Anatomical Therapeutic Class

CRF Case Report Form

CRP C-Reactive Protein

CPK Creatine Phosphokinase

DB Double-Blind

ECG Electrocardiogram

EDC Electronic Data Capture

FDA US Food and Drug Administration

GCP Good Clinical Practice

hs-CRP High Sensitivity C-Reactive Protein

ICH International Conference on Harmonization

ICH E8 General Considerations for Clinical Trials

ICH E9 Statistical Principles for Clinical Trials

IDMC Independent Data Monitoring Committee

FAS Full Analysis Set

LOCF Last Observation Carried Forward

MedDRA Medical Dictionary for Regulatory Activities

MMRM Mixed model of repeated measures

MNAR Missing Not At Random

OL Open-Label

OC Observed Case

PCS Potentially Clinically Significant

PD Pharmacodynamics

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PK Pharmacokinetics

PMN Pattern Mixture Model

PPS Per Protocol Set

QOL Quality of Life

SAE Serious Adverse Event

SAP Statistical Analysis Plan

SmPC Summary of Product Characteristics

SOC System Organ Class (used in MedDRA dictionary)

TEAE Treatment Emergent Adverse Event

TLF Tables, Listings, and Figures

USPI United States Package Insert

WC Worst Case

WHO World Health Organization

11/23/2020

1 INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of efficacy and safety as outlined and/or specified in the final study protocol. Specifications of tables, figures, and data listings are contained in a separate document (Table shells).

A separate pooled-analysis SAP for pre-specified analysis based on adjudicated composite safety data will complement this study specific SAP. This SAP is based on the Amendment 4 of the protocol dated September 20, 2017.

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

Evaluate the efficacy and safety of roxadustat in the treatment of anemia in incident dialysis subjects compared to active control (Epoetin alfa).

2.2 SECONDARY OBJECTIVES

- Evaluate the utilization of intravenous (IV) iron with roxadustat compared to active control
- Evaluate the effect of roxadustat on serum lipid parameters compared to active control
- Evaluate the effect of roxadustat on blood pressure (BP) compared to active control
- Evaluate time to achieve hemoglobin (Hb) response compared to active control

3 STUDY DESIGN

This is a Phase 3, multicenter, randomized, open-label, and active-controlled study to evaluate the efficacy and safety of roxadustat in incident dialysis subjects with anemia.

A total of up to 1,200 subjects are planned to be randomized to receive roxadustat or epoetin alfa (active control) in a 1:1 ratio, respectively.

Randomization stratification factors include geographical region (US vs. Ex-US), screening Hb values (≤8 g/dL vs. >8 g/dL), and cardiovascular/cerebrovascular/thromboembolic medical history (yes vs. no).

In addition, the change of protocol were incorporated via amendments on 20 Oct 2014, 24 Nov 2015, 12 Aug 2016, and current one on 20 September 2017.

Subjects randomized to roxadustat will have doses administered thrice weekly (TIW) throughout the Treatment Period using an initial tiered, weight-based, dosing scheme (see Table 1 below), followed by dose titration every 4 weeks.

Table 1. Initial Study Drug Dosing

Study Drug (Dose Frequency)	Low Weight/Dose	Median Weight/Dose	High Weight/Dose	
Roxadustat (TIW) – Original Protocol	45 to 60 kg/70 mg	>60 to 90 kg/100 mg	>90 to 160kg/150 mg	
Roxadustat (TIW) – Amended Protocol	≤ 70 kg/70 mg >70 to 160 kg/100 mg			
Epoetin alfa HD (TIW)	IV dosing according to epoetin alfa USPI or SmPC			
Epoetin alfa PD (TIW)	Epoetin alfa should be administered according to epoetin alfa USPI or SmPC or local standard care.			
	Abbreviations: HD = hemodialysis; IV = intravenous; PD = peritoneal dialysis; SmPC = summary of product characteristics; TIW = three times a week; USPI = United States Package Insert; wt = weight. Note: Weight in HD subjects = subject's dry weight.			

The study periods are as follows:

- Screening Period: Up to 6 weeks
- Treatment Period: Treatment duration is variable for individual subjects with maximum treatment duration of up to approximately 3 years after the last subject is randomized. The minimum treatment duration may be less than 52 weeks.
- Post-Treatment Follow-Up Period: 4 weeks

Dose Adjustments

Roxadustat arm

Dose adjustments will occur in two separate study dosing phases: the Correction Phase and the Maintenance Phase. Each of these phases will follow unique dose adjustment rules according to Appendix 2 in the amended protocol of 20 October 2014. All subjects in the roxadustat arm will be dosed orally TIW during the Treatment Period. The maximum roxadustat dose is 3.0 mg/kg per dose or 400 mg, whichever is lower.

All dose adjustments as well as assessments of predefined out of range hemoglobin elevations are based on Hb values using a point-of-care device such as HemoCue® or CritLine®. In the event that the central lab Hb value of the site visit is significantly different and the dose adjustment decision based on the HemoCue® or CritLine® value is being reconsidered, the Medical Monitor should be contacted, if possible. The determination of Hb response and transition from the Correction to the Maintenance Phase of the study is based on the central laboratory Hb value.

Active Control arm

For subjects receiving Active Control, dose adjustment rules are implemented according to the epoetin alfa US Package Insert (USPI) or Summary of Product Characteristics (SmPC).

Correction Phase of Dosing

Roxadustat arm

The aim of the Correction Phase is to increase Hb levels from baseline to the desired Hb level defined as a responder in Section 4.1 by using the dose adjustment algorithm in appendix 2 of the amended protocol of 20 September 2017. This phase is variable in length for each subject.

Maintenance Phase of Dosing for Roxadustat Arm

The aim of the Maintenance Phase is to maintain Hb levels after the initial correction by using the dose adjustment algorithm in appendix 2 of the amended protocol of 20 September 2017.

Dosing and Dose Adjustment for Active Control Arm (Epoetin alfa)

Subjects on epoetin alfa should maintain their Hb levels within the target range accepted by their health authorities, specifically:

- Hb 10 to 11 g/dL in the United States
- Hb 10 to 12 g/dL in countries outside the United States

Subjects receiving HD on epoetin alfa will be dosed IV TIW, with starting doses and dose adjustment rules according to the epoetin alfa USPI or SmPC.

Subjects receiving PD on epoetin alfa will be dosed according to the epoetin alfa USPI or SmPC, or local standard of care.

For countries using prefilled syringes, the initial epoetin alfa dose and dose adjustments should be approximated to the closest calculated weekly dose.

4 STUDY ENDPOINTS

4.1 PRIMARY EFFICACY ENDPOINT

There are 2 separate primary endpoints which are defined for US (FDA) submission and Ex-US submission respectively.

US (FDA) submission.

The primary efficacy endpoint for the US submission is the Mean Hb change from baseline (using central laboratory values) to the average level during the Evaluation Period, defined as Week 28 until Week 52. This analysis will be based on the intent-to-treat (ITT) population. Hemoglobin values under the influence of rescue therapy (see definition below) will not be censored for the primary analysis.

Ex-US submission

The primary efficacy endpoint for the Ex-US submission is defined as the proportion of subjects who achieve a Hb response at two consecutive visits at least 5 days apart during the first 24 weeks of treatment, without rescue therapy (see definition below) within 6 weeks prior to the Hb response in the Per Protocol Set (PPS). A Hb response is defined, using central laboratory values, as:

- Hb \geq 11.0 g/dL and a Hb increase from baseline by \geq 1.0 g/dL in subjects whose baseline Hb \geq 8.0 g/dL, or
- Increase in Hb \geq 2.0 g/dL in subjects whose baseline Hb \leq 8.0 g/dL.

Rescue therapy for roxadustat treated subjects is defined as recombinant erythropoietin or analogue (ESA) or RBC transfusion, and rescue therapy for Epoetin alfa treated subjects is defined as RBC transfusion. All endpoints using Hb are based on the central lab data.

Baseline Hb is defined as the mean of at least the last 3 available central laboratory Hb values prior to first dose of study medication: three last screening Hb values plus the predose Hb value collected on day 1. In subjects with missing Day 1 Hb value, the mean of three last screening laboratory Hb values will be considered as baseline Hb value.

Hb values from the central laboratory will be sorted by visit date. If two consecutive ontreatment Hb values from the central laboratory meet the Hb response criteria defined by primary efficacy endpoint for the Ex-US submission, the subject will qualify for Hb response as long as there is no rescue therapy 6 weeks before the date of the first of these 2 Hb measurements.

The classification of Hb response shall take into account all consecutive Hb values regardless of whether they are obtained at scheduled or unscheduled visits.

RBC transfusion is collected in the Blood Transfusions form of the eCRF. The use of ESA is recorded in the related forms of the eCRF and coded into ATC (Code: B03XA01) and generic name.

4.2 ALTERNATIVE DEFINITIONS OF THE PRIMARY EFFICACY ENDPOINT

4.2.1 Hb Response Regardless Use of Rescue Medication (for Sensitivity Analysis)

An alternative definition of the Hb response, for sensitivity analysis purposes, is defined as:

- Hb \geq 11.0 g/dL and a Hb increase from baseline by \geq 1.0 g/dL in subjects whose baseline Hb >8.0 g/dL, or
- Increase in Hb \geq 2.0 g/dL in subjects whose baseline Hb \leq 8.0 g/dL.

at two consecutive visits with at least 5 days apart within the first 24 weeks of treatment regardless use of rescue therapy. Subjects who discontinue study medication before Hb response, as defined above, will be considered as non-responder.

4.3 SECONDARY EFFICACY ENDPOINTS

The secondary efficacy endpoints are for both US and Ex-US submissions unless specified otherwise:

US (FDA submission): The proportion of subjects who achieve a Hb response at two consecutive visits with at least 5 days apart during the first 24 weeks of treatment, without rescue therapy within 6 weeks prior to the Hb response. This analysis will be based on the ITT Population.

A Hb response is defined, using central laboratory values, as

- Hb \geq 11.0 g/dL and a Hb increase from baseline by \geq 1.0 g/dL in subjects whose baseline Hb > 8.0 g/dL, or
- o Increase in Hb \geq 2.0 g/dL in subjects whose baseline Hb \leq 8.0 g/dL

Ex-US submission: Mean Hb change from baseline to the average level during the Evaluation Period, defined as Week 28 until Week 36 without rescue therapy within 6 weeks prior to and during the evaluation period. This analysis will be based on the PPS population.

- The time to achieve the first hemoglobin (Hb) response defined by the primary endpoint for Ex-US or the first secondary efficacy endpoint for the US submission.
- Proportion of patient exposure time (months) with Hb>= 10 g/dL during Weeks 28-52, similarly analysis for the period between Weeks 28 36
- Mean change from baseline in Low-density lipoprotein (LDL) cholesterol averaged over Weeks 12-24
- Mean change from baseline in Hb levels between Weeks 18 to 24 in patients whose baseline hs-CRP> ULN
- Average monthly IV iron use per subject during weeks 28-52
- Time to first RBC transfusion during the treatment
- Mean change in mean arterial pressure (MAP) averaged over Weeks 8-12

• Time to first exacerbation of hypertension (defined as [systolic BP≥170 mmHg AND systolic BP increase from BL≥20 mmHg] or [diastolic BP≥110 mmHg AND diastolic BP increase from BL≥15 mmHg]) during weeks 28 to52

4.4 ADDITIONAL EVALUATION OF EFFICACY

The additional efficacy evaluations in this study are:

Hb Correction and Maintenance:

- Hemoglobin maintenance: Mean change from baseline in Hb averaged over 8 weeks of treatment at Weeks 28 to 36, without rescue therapy within 6 weeks prior to and during this 8-week evaluation period.
- Hemoglobin long-term Maintenance: Mean change in Hb averaged over 8 weeks of treatment at Weeks 44-52 without rescue therapy within 6 weeks prior to and during this 8-week evaluation period.
- Mean change from baseline in Hb averaged over the 96 to 104 weeks of treatment, without rescue therapy within 6 weeks prior to and during this 8-week evaluation period.
- Change from baseline in Hb at each of the selected post-dosing time points.
- Proportion of subjects with Hb >=10 g/dL averaged over Weeks 28-36, without rescue therapy within 6 weeks prior to and during this 8-week evaluation period.
- o Proportion of subjects with mean Hb < 9 g/dL, 9-<10, 10-<11, 11-<12, 12-<13, >=13 g/dL during Weeks 28-36
- Proportion of patient exposure (PEY) with Hb < 9 g/dL, 9-<10, 10-<11, 11-<12, 12-<13, >=13 g/dL during weeks 28 to 52

Hospitalizations:

- o Time to first hospitalization (% of subjects) up to Week 52.
- Time to first hospitalization or skilled nursing facility (% of subjects) up to Week 52
- o Number of days of hospitalizations per patient-exposure year (PEY).
- Number of days of hospital or skilled nursing facility per PEY
- Number of medical-facility free days (hospital, skilled nursing facility, emergency room, or overnight observation) per PEY
- Number of days on treatment out of hospital and skilled nursing facility up to Week 52, 7 days after Last Dose.

Missed dialysis sessions up to Week 52

- o Occurrence (number) of missed dialysis sessions
- o Proportion of subjects with missed dialysis sessions
- Number of days of missed dialysis sessions per patient-exposure year (PEY)

• Rescue Therapy Use up to Week 52:

- Proportion of subjects who receive RBC transfusions.
- o Number of RBC packs per patient-month exposure to study medication.
- Roxadustat subjects: The proportion of subjects requiring ESA rescue therapy (ATC code: B03XA01)

• Changes in Cholesterol Levels:

- O Change at each of the protocol specified treatment time points in:
 - total cholesterol,
 - low-density lipoprotein (LDL)/high-density lipoprotein (HDL) ratio,
 - non-HDL cholesterol.
- Proportion of subjects achieving LDL target of <100 mg/dL averaged over Weeks 12-24 of treatment.

Blood Pressure Effect:

- o Time to an exacerbation of hypertension over weeks 28-52, meeting at least 1 of the following criteria: Increase in blood pressure: An increase from baseline of ≥ 20 mm Hg systolic BP and sBP >170 mmHg or an increase from baseline of ≥ 15 mm Hg diastolic BP and dBP>100 mmHg.
 - Proportion of subjects achieving blood pressure treatment goal in ESRD subjects (pre dialysis systolic BP <140 mmHg and diastolic BP<90 mmHg) averaged over Weeks 12-28.

• Health Related Quality of Life (HRQoL) and EQ-5D-5L Benefits of Anemia Therapy:

Mean change averaged over Weeks 12, 36 and 52 of treatment including those listed below.

- Vitality Sub-score of SF-36:
 - In FAS subjects with baseline Vitality Sub-score below 50.
 - In all FAS subjects.
- Physical Functioning Sub-scores of SF-36:
 - In FAS subjects with baseline *Physical Functioning Subscores* below 40.
 - In all FAS subjects.
- Anemia Subscale ("Additional Concerns") of Functional Assessment of Cancer Therapy-Anemia (FACT-An) Scores:
 - In FAS subjects with baseline subscale scores below 55 (generally associated with fatigue).
 - In all FAS subjects.

- o Total FACT-An Scores:
 - In FAS subjects with baseline FACT-An scores below 135
 - In all FAS subjects.
- EQ-5D-5L Scores and other QoL Measures/Other Component scores of SF-36: In all FAS subjects.

• Hepcidin, Iron, CHr and HbA1c:

- Change from baseline in serum hepcidin at each of the selected time points (e.g., Weeks 4, 12, 20, 44 and every 8 weeks onwards)
- Change in serum iron from baseline to Week 28
- Change in TSAT from baseline to Week 28
- Change from baseline in serum ferritin at each of the selected time points, total and sub-grouped by baseline values of, >=400 ng/mL, 400 to 100 ng/mL, and <100 ng/mL.
- Change from baseline in TSAT at each of the selected time points, total and sub-grouped by baseline values of $\geq 40\%$, 40% to 20%, and $\leq 20\%$.
- Serum iron at each of the time points tested
- Change from baseline in CHr at each of the selected time points (e.g., Weeks 4. 8, 12, 20, 28, 36 and every 8 weeks onwards)
- Proportion of patients with CHr > LLN at each timepoint tested: Weeks 4, 8, 12, 20, 28, 36, and every 8 weeks onwards)
- Change from baseline in HbA1c level at each of the selected time points in subjects without history of diabetes, in subjects with history of diabetes, and all subjects.
- Changes from BL to each study visit (when measured) in fasting blood glucose,

4.5 SAFETY ASSESSMENTS

Study-specific safety will be assessed by evaluating the following:

- Occurrence of treatment emergent adverse events (TEAEs), treatment emergent serious adverse events (TESAEs) and clinically significant laboratory values
- Changes from Baseline in vital signs, electrocardiogram (ECG) findings, and clinical laboratory values.
 - Safety interpretation will also be made based on analyses of composite endpoints derived from pre-specified and adjudicated events pooled across multiple studies in the roxadustat Phase 3 program. The members of an independent adjudication committee blinded to treatment assignment will adjudicate the following events in multiple phase 3 studies. Death from any cause, MI, stroke, heart failure requiring hospitalization, unstable angina requiring hospitalization, hypertensive emergency, deep venous thrombosis, pulmonary embolism, and vascular access thrombosis.

• Safety analyses based on these adjudicated events will be pooled across multiple studies. The analyses of the adjudicated events will be detailed in the pooled SAPs.

5 GENERAL STATISTICAL CONSIDERATIONS

5.1 SAMPLE SIZE DETERMINATION

The sample size calculation is based on the primary endpoints for the US (FDA) submission and Ex-US submission.

During the course of this study, which is being conducted in parallel with other Phase 3 studies, approximately 1000 subjects were to be enrolled to contribute to safety evaluation of roxadustat in comparison to epoetin alfa in CKD patients on dialysis less than 6 months. The final number of patients to be enrolled in this study will be based on the enrollment rate of other roxadustat phase 3 studies on dialysis patients, in order to optimize program timeline to generate sufficient adjudicated safety data across dialysis studies.

With at least 600 subjects, the study will provide at least 99% power to demonstrate statistical non-inferiority of roxadustat versus ESA in the primary endpoint for US (FDA) submission (i.e., specifically, Hb change from baseline to the average level during the evaluation period defined as Week 28 until Week 52). This assumes a difference (roxadustat minus ESA) of -0.30 g/dL, a non-inferiority margin for this difference of -0.75 g/dL (see Appendix 6 for the NI margin justification) and a standard deviation of 1.25 g/dL. This endpoint will be analyzed using the ITT population for the US (FDA) submission.

The study will provide at least 99% power to demonstrate statistical non-inferiority of roxadustat versus ESA in the primary endpoint outside of the United States (i.e., specifically, the proportion of subjects who achieve a Hb response at two consecutive visits during the first 24 weeks of treatment, without rescue therapy within 6 weeks prior to the Hb response). This assumes an 80% responder rate for both roxadustat and epoetin alfa, in order to support the primary efficacy analysis (i.e., a non-inferiority comparison in responder rate between roxadustat and epoetin alfa) and assuming a non-inferiority margin of -15% for this difference (roxadustat minus epoetin alfa).

Appendix 6 has description on the justification that the non-inferiority margin that were used.

5.2 ANALYSIS POPULATIONS

5.2.1 Intent-to-treat (ITT) Population

The ITT population will consist of all randomized subjects. If treatment received differs from the randomized treatment, the randomized treatment assignment will be used.

5.2.2 Safety Population

The Safety Population will consist of all randomized/enrolled subjects who received at least one dose of study medication. If treatment received differs from the randomized treatment, the actual treatment will be used for the safety analysis.

5.2.3 Full Analysis Set (FAS)

The FAS population will consist of all randomized/enrolled subjects who received at least one dose of study drug and have at least one post-dose Hb assessment. If treatment received differs from the randomized treatment, the randomized treatment assignment will be used for efficacy analysis.

5.2.4 Per Protocol Set (PPS)

The PPS population will consist of all subjects in the FAS population who received at least 8 weeks of treatment, have at least one valid post-dose Hb assessment and are without major protocol violations.

5.2.5 Major Protocol Deviations

Major protocol deviations of interest may include, but are not limited to the criteria in Table 2.

A subset of pre-specified major protocol deviations will exclude some patients in the PPS analyses. These will be identified while data are collected prior to database lock. Considerations will be given according to the following table.

Table 2. Criteria for Assessing Major Protocol Deviations

Number	Major Protocol Deviation
1	Violation of key* inclusion or exclusion criteria which may affect the assessment of the
	efficacy of the study drug
2	Administration of wrong randomization study drug for more than 4 week before week 24; any
	duration from week 24 to week 52
3	Study drug compliance < 75% (up to Week 52)
4	Administration of prohibited concomitant medication that may impact evaluation of efficacy of
	the study drug*
5	Significant noncompliance with study procedures that may impact evaluation of efficacy of the
	study drug will be evaluated case by base*

^{*}Subject to Medical Monitor's decision

The number and percentage of major protocol deviations will be categorized and summarized by treatment group as deemed appropriate.

5.3 METHODOLOGY AND CONVENTIONS

Safety and efficacy data will be summarized and presented by treatment group and time point in summary tables. Continuous variables will be presented by descriptive statistics: n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be tabulated by frequency count and percentage.

Lab results obtained from the central laboratory, rather than local laboratories, will be used for all efficacy and safety analyses. Local laboratory values, if collected in the CRF's, will be listed only in data listing.

When the actual treatment received by a subject is different from the randomized treatment assigned, the subject will be analyzed per the randomized treatment for the efficacy parameters; while they will be analyzed per actual treatment that was taken for the safety parameters for US submission.

Unless otherwise stated, all statistical tests will be two-sided hypothesis tests performed at the 5% level of significance for main effects and all confidence intervals will be two-sided 95% confidence intervals.

The secondary endpoints will be tested sequentially using the fixed sequence approach for multiplicity adjustments at an alfa level of 0.05. There will be no adjustments for multiple comparisons for other tests.

All analyses will be performed using SAS® Version 9.1.3 or higher.

5.4 ADDITIONAL DATA HANDLING RULES AND PRESENTATION SPECIFICATIONS

The following general guidelines will apply to all statistical analyses and data presentations:

- Baseline is defined as the last available value obtained prior to the first dose of study drug, unless otherwise specified in this SAP.
- Hb baseline is defined as the mean of the at least last three available values obtained prior to the first dose.
- Baselines for reticulocyte count, reticulocyte hemoglobin content (CHr), hepcidin, serum iron parameters (transferring, TIBC, TSAT, Ferritin, sTfR, and iron), lipids, blood pressures and heart rate are defined as the mean of values obtained within 6 weeks prior to the first dose.
- Randomization stratification factors and enrollment protocol version derived from actual data (not the ones from the randomization system) will be used in all applicable analysis models.

The stratification factors to be used in efficacy analyses are:

- 1. Us vs Ex-US Screening Hb values (≤ 8 g/dL vs. > 8 g/dL) (other than Hb related endpoints)
- 2. Cardiovascular/cerebrovascular/thromboembolic medical history (Yes vs. No)
- 3. Geographic Region
- 4. The original protocol and amended protocols
- Unscheduled visits within an allowable window will be grouped into the closest scheduled visits based on the visit window specified in Appendix 1. For subjects who have more than one measurement at a certain scheduled visit, the last measurements

- will be used, with the exception of CPK, WBC, liver function tests (i.e., ALT, AST, GGT, ALP, and total bilirubin), in which the maximum measurement will be used.
- By default, US conventional units will be used for laboratory value presentations. A set of lab summary tables in SI units will also be provided based on TLF index.
- Age is calculated as of date that the informed consent form was signed.
 age = INTCK('YEAR', Birth date, date of Informed Consent, 'C') where INTCK is a SAS function.
- Duration of treatment or days in treatment is calculated as: last dose date first dose date +1
- Body weight, height and temperatures will converted using the following formula:
 - kg = 1b/2.2
 - -cm = 2.54 x in
 - $C^{\circ} = (5/9) \times (F^{\circ} 32)$
- The mean, standard deviation and median will be presented with adding one more decimal to raw data with rounding off. The minimum and maximum will be presented with the same number of decimals as in the raw data.
- All percentages will be rounded to one decimal place and lined up by the decimal place. The percentage will be suppressed when the count is zero.
- Any p-values will be rounded to four decimal places and will be presented as '<.0001' if they are less than 0.0001 after rounding.
- All tables and listings will have a header showing "FibroGen, Inc.", the protocol number, and Page x of y. Footer will indicate the program file path/name, run date and run time.
- For continuous variables that are recorded as "< X" or "> X", the value of "X" will be used in the calculation of summary statistics. The original values will be used for the listings.
- Decimal points will be presented as follows: N will be presented without decimal, minimum and maximum in same precision as in the database, mean and median in one more decimal than minimum and maximum, and SD in one more decimal than mean and median.
- Tables and figures will use derived analysis visit. Listings will use nominal visits, show the flag to indicate analysis visit to be used. Namely, both Nominal visit and analysis visit will be presented in the listing.
- Additional data handling conventions are detailed in Appendix 1.

6 SUBJECT ACCOUNTABILITY AND DISPOSITION

The following subject data will be summarized and presented by treatment group (roxadustat and active control) if applicable:

- Number and percentage of subjects screened and randomized (using the screened subjects population)
- Number and percentage of subjects randomized at each center, and for all centers combined, by treatment group (using the ITT population)
- Number and percentage of subjects in each analysis set, by treatment group (using the ITT population)

- Number and percentage of subjects excluded from the Per Protocol analysis set by reason for exclusion, treatment group (using the ITT population)
- Kaplan-Meier plots will be generated for premature treatment discontinuation by randomization arm showing 2 curves (one curve per treatment group).
- All subjects who prematurely discontinued during the treatment period will be listed by discontinuation reason for the randomized population.

7 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters and important baseline and disease characteristics will be summarized by treatment group for the ITT, Safety, FAS and PPS populations. These include but may not be limited to age, age group (18 to 64, 65 to 74, \geq 75), sex, ethnicity, race, region, weight, body-mass index (BMI), Hemoglobin, baseline Hb categories, iron repletion status at baseline, Ferritin, Ferritin group (<100 vs. >=100 ng/mL), TSAT and TSAT group (<20% vs. >=20%), iron deplete (ferritin >=100 and TSAT >=20%) vs. not, cHepcidin< eligibility threshold or not, baseline C-reactive protein (CRP) group (CRP \leq ULN vs. CRP > ULN), cardiovascular or cerebrovascular or thromboembolic medical history (yes vs. no), primary reason for CKD/ESRD as one of the baseline characteristics (DM and HPT vs. all others).

In addition, 25%-75% values of Hb and platelets will be presented. Frequency distributions (number and percentage of subjects) will be presented for categorical variables.

The baseline characteristics, iron indices, and iron IV given between ESA naïve and those treated with ESA then washed out will be summarized and presented in a table.

Descriptive statistics of baseline values for other parameters will be presented in their change from baseline tables.

A summary table for the patient population for enrolled patients before and after the protocol amendments will be presented.

8 MEDICAL HISTORY

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Medical History of interest including Chronic Kidney Disease (CKD) History inclusive of CKD Cause, Cardiovascular Disease, Cerebrovascular Disease, Thrombosis History, Hypertension History, Diabetes History, and Anemia History will be summarized by system organ class, preferred term and treatment group for the Safety Population.

9 STUDY MEDICATION

9.1 EXTENT OF EXPOSURE

Exposure to study medication will be summarized by treatment group in terms of treatment duration in weeks, which is calculated using the following formula: (the date of last medication taken - the date of first dose taken +1)/7.

Total weekly study drug exposure is defined as the total prescribed dose (in mg and mg/kg for Roxadustat and IU and IU/kg for EPO) of study drug administered within the week (windowed by 7-day period from Day 1).

Duration of exposure, weekly exposure and total study drug exposure will be tabulated by treatment group for the safety population.

Per administration amount and administration frequency will also be tabulated by treatment group for the safety population and PPS population.

Patient-Exposure-Year (PEY) is defined as (Last Dose Date – First Dose Date + 1)/365.25.

9.1.1 Dosing Changes

Dosing changes for both treatment groups are collected in the Study Drug Administration/HemoCue/Dose Adjustment Form in the eCRF. Two types of dosing changes will be calculated.

A dose-per-intake change is the change in the number of milligrams on the intake day (for example from 200 mg TIW to 250 mg TIW). A weekly-dose change is the change in the prescribed weekly dose, calculated as the dose-per-intake times the weekly frequency.

For example a change from 200 TIW to 250 TIW is a change of 600 mg to 750 mg per week which is considered as a change in dose-per-intake and a change in weekly-dose as well.

For each subject the total number of dose-per-intake changes and the weekly-dose changes will be calculated.

9.1.2 **Duration of Exposure**

Exposure time will be categorized according to the following categories by treatment groups (roxadustat and ESA):

- Less than 2 weeks
- At least 2 weeks, less than 4 weeks
- At least 4 weeks, less than 26 weeks
- At least 26 weeks, less than 52 weeks
- At least 52 weeks, less than 78 weeks
- At least 78 weeks, less than 104 weeks
- At least 104 weeks, less than 130 weeks
- At least 130 weeks, less 156 weeks
- More than 156 weeks
- Unknown

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9.2 TREATMENT COMPLIANCE

Study medication dosing compliance for a specified period is defined as the total dose (mg actually taken by a patient during that period divided by the prescribed dose expected to be taken during the same period multiplied by 100. An overall per-dose compliance measure can be calculated by (# of actual dose administrations)/ (Total # of expected dose administrations) *100 during the subject's treatment period. Descriptive statistics for study medication compliance will be presented by treatment group for the entire treatment period of the study.

Compliance will be summarized as follows:

- Descriptive statistics will be summarized by the 2 treatment groups for entire treatment period.
- Percent compliance will be categorized according to the following categories for entire treatment period for safety population by the 2 treatment groups:
 - o less than 50% (significant drug noncompliance)
 - o at least 50%, less than 75% (moderate drug noncompliance)
 - o greater or equal 75% (drug compliance)
 - o unknown

10 PRIOR AND CONCOMITANT MEDICATIONS

The World Health Organization Drug Dictionary (WHO Drug) will be used to classify prior and concomitant medications by therapeutic class and generic name based on ATC code level 3. Prior medication is defined as any medication taken and stopped prior to the first dose of the study medication. Concomitant medication is defined as any medication taken between the day of first dose of the study medication and the day of last study medication date + 28 days.

Medication start and end dates and times will be compared with the start date of study drug and classified as per Table 3.

In case of partial or missing dates, comparisons will be made based on the level of detail available. For example, if start date of study drug is 04Jan2013, and a medication has a start date of Jan2013 but missing day, the medication will be classified as concomitant.

Table 3: Classification of prior and concomitant medications

End date Start date	Before start of study drug administration	On or after start of study drug administration	Missing
Before start of study drug administration	Prior	Concomitant	Concomitant
On or after start of study drug administration	_	Treatment Emergent Concomitant	Treatment Emergent Concomitant
Missing	Prior	Concomitant	Concomitant

Both prior and concomitant medication usage will be summarized by the number and proportion of subjects in each treatment group. Subjects will only be counted one time in each unique ATC Class and generic name if multiple drugs are used by a subject.

Detailed analyses may be performed on prior and concomitant medications of special interests such as oral iron, blood pressure medications and lipids medications.

11 EFFICACY ANALYSES

Efficacy analysis will be conducted on the ITT and FAS for US (FDA) submission and analysis for non-inferiority on the PPS population and analysis for superiority on FAS population for EU regulatory submission.

The **Efficacy Emergent Period** is defined as the evaluation period from the Analysis date of first dose intake up to 7 days after the Last Dose of study drug or EOT Visit, whichever occurs first. This period will be used as reference period for the time to event analyses related to efficacy endpoints, unless specified otherwise.

11.1 ANALYSIS OF PRIMARY ENDPOINT

11.1.1 Primary Endpoint

There are 2 primary efficacy endpoints: one for the US submission and one for the Ex-US submission.

The primary efficacy endpoint for the US submission is the Mean Hb change from baseline (using central laboratory values) to the average level during the Evaluation Period, defined as Week 28 until Week 52. This analysis will be based on the intent-to-treat (ITT) population. Hemoglobin values under the influence of rescue therapy will not be censored for the primary analysis.

The primary efficacy endpoint for the Ex-US submission is defined as the proportion of subjects who achieve a Hb response at two consecutive visits during the first 24 weeks of treatment, without rescue therapy within 6 weeks prior to the Hb response. This analysis will be based on the PPS population.

- A Hb response is defined, using central laboratory values, as: Hb≥11.0 g/dL and a
 Hb increase from baseline by ≥1.0 g/dL in subjects whose baseline Hb>8.0 g/dL,
 or
- Increase in Hb \geq 2.0 g/dL in subjects whose baseline Hb \leq 8.0 g/dL.

Rescue therapy for roxadustat treated subjects is defined as ESA rescue or RBC transfusion, and rescue therapy for Epoetin alfa treated subjects is defined as RBC transfusion.

11.1.2 Primary Analysis

Efficacy analysis for superiority will be conducted on the ITT population for US (FDA) submission and on the FAS population for Ex-US submission.

Efficacy analysis for non-inferiority will be conducted on the ITT population for US (FDA) submission and on the PPS population for Ex-US submission.

<u>US (FDA) Submission</u>: The primary efficacy endpoint for US (FDA) submission is defined as the mean Hb change from baseline to the average level during the Evaluation Period, defined as Week 28 until Week 52. The analysis will be based on the ITT

population. Hb values under the influence of rescue therapy will not be censored for the primary efficacy analysis.

The primary hypothesis to be tested for the primary efficacy analysis is:

 H_0 : Hb mean change from baseline to the average level from Week 28 to Week 52 in the roxadustat arm \leq Hb mean change from baseline in the epoetin alfa arm minus 0.75 g/dL

Versus:

 H_1 : Hb mean change from baseline to the average level of Week 28 to Week 52 in the roxadustat arm > Hb mean change from baseline in the epoetin alfa arm minus 0.75~g/dL

A multiple imputation analysis of covariance (MI ANCOVA) model will be used. The model will contain terms for treatment group, baseline Hb measurement, and stratification factors except Screening Hb values (≤ 8 g/dL vs. > 8 g/dL). The primary efficacy analysis will be based on the estimated difference between the two treatments overall mean effects throughout the evaluation period based on the pooled ANCOVA model.

This null hypothesis will be rejected if the two-sided 95% CI for the difference between the two treatment groups using MI ANCOVA model lies entirely above -0.75 g/dL.

The following steps will be used to conduct the primary analysis of the primary endpoint:

- 1. Generate 200 datasets, using seed 162345 for the U.S., where only intermittent missing hemoglobin data will be imputed for each treatment relying on non-missing data from all subjects within each treatment group using the Monte Carlo Markov Chain (MCMC) imputation model baseline hemoglobin, and the available non missing hemoglobin for each scheduled Week by treatment group.
 - The MCMC statement in the SAS PROC MI procedure with monotone option will be used. As a result, each dataset will only have missing ending data, or a monotone missing data pattern.
- 2. For each dataset from step 1, missing ending data (hemoglobin up through end of evaluation period) will be imputed. As a result, 200 imputed complete datasets will be generated.
 - Missing data at Week 1 will be imputed using the regression imputation model with baseline stratification factor, baseline and hemoglobin from Week 1, using the SAS PROC MI procedure with the REGRESSION option in the MONOTONE statement.
 - The SAS PROC MI procedure will use data separately from each treatment subjects to impute the missing data for a specific Week (i.e. only those that need the imputation for the Week). Since subjects from the different treatment groups for that Week are excluded from the step, they will not contribute to the imputation for the Week.
- Repeat for all other scheduled Weeks sequentially (Week 2 to the end of evaluation period). Subjects whose missing data were imputed for previous Weeks will contribute to the imputation for the current Week.

- The regression imputation model includes an intercept and the slopes of the hemoglobin from previous Weeks.
- 3. Analyze each imputed complete dataset using the ANCOVA model using the mean of all observed or imputed Hb values within the evaluation period (Week 28 − 52). The model will contain terms for baseline Hb measurement as a covariate, treatment group and stratification factors except Screening Hb values (≤ 8 g/dL vs. > 8 g/dL) as fixed effects.

Sample SAS code:

```
PROC MIXED data=xx;
class treatment categorical covariates;
model change_Week36 = treatment covariates / solution;
lsmeans treatment / diff cl;
ods output Diffs=lsdiffs LSMeans=lsm solutionF=Parms;
by _Imputation_;
run;
```

4. Combine estimates from the results for each of the 200 ANCOVA model using SAS PROC MIANALYZE.

```
PROC MIANALYZE parms(classvar=full)=lsdiffs; class treatment categorical covariates; modeleffects treatment; ods output ParameterEstimates=MIAN_lsdiffs; run;
```

Report the results of the least-squares mean estimates of the change from baseline in hemoglobin during the evaluation period, the estimates of treatment effect (e.g. least-squares mean CFB in hemoglobin for the treatment group minus the least-squares mean CFB in hemoglobin for the active comparator group) and the corresponding p-values during the evaluation period.

The analysis will be repeated with Hb values under the influence of rescue therapy censored Namely, set Hb to missing for Rescue Medication and 6 weeks afterwards (or 8 weeks if during the evaluation period).

Ex-US Submission: The primary efficacy endpoint for Ex-US submission is defined as the proportion of subjects who achieve an Hb response at two consecutive visits during the first 24 weeks of treatment, without rescue therapy within 6 weeks prior to the Hb response.

- A Hb response is defined, using central laboratory values, as: Hb \geq 11.0 g/dL and a Hb increase from baseline by \geq 1.0 g/dL in subjects whose baseline Hb > 8.0 g/dL, or
- Increase in Hb \geq 2.0 g/dL in subjects whose baseline Hb \leq 8.0 g/dL

Rescue therapy for roxadustat treated subjects is defined as ESA rescue or RBC transfusion, and rescue therapy for epoetin alfa treated subjects is defined as RBC transfusion. The hypothesis to be tested for the primary efficacy analysis is:

 H_0 : Hb response rate for subjects in the roxadustat arm - Hb response rate for subjects in the epoetin alfa arm \leq -15%

Versus

 H_1 : Hb response rate for subjects in the roxadustat arm - Hb response rate for subjects in the epoetin alfa arm > -15%

A two-sided 95% CI for the difference of 2 responder rates (roxadustat minus epoetin alfa) based on the Miettinen & Nurminen approach adjusting for treatment and stratification factors will be calculated and this null hypothesis will be rejected if the lower bound of the 95% CI is greater than -15%. Subjects who dropped out from the study without data for the assessment will be treated as non-responder.

11.1.3 Sensitivity Analyses of Primary Endpoint

The following secondary analyses will be performed on the U.S. primary efficacy endpoint as sensitivity analyses to examine the potential impact of missing data on the estimates. These analyses will be performed using ITT Population. The results of the analyses will be summarized in Table 4. These sensitivity analyses are further detailed in each Section.

 $df = (m-1)\left(1 + \frac{m\overline{U}}{(m+1)B}\right)^2.$ where B is

Table 4: U.S. Primary Endpoint Analysis Results

Analysis (ITT Population)	Trt Diff and 95% CI (roxadustat vs EPO)	Std. Err.	Degree of Freedom*	t-statistics	p-value
ANCOVA with Multiple Imputations (Primary)	.xx (.xx, .xx)	.xx	XXX	.xxx	.xxxx
ANCOVA-MI with Hb censored**for rescue therapy	.xx (.xx, .xx)	.XX	xxx	.xxx	.xxxx
MMRM	.xx (.xx, .xx)	.XX	XXX	.XXX	.xxxx
PMM-Last Mean Carried Forward	.xx (.xx, .xx)	.XX	XXX	.XXX	.xxxx
PMM –Baseline Carried Forward (Roxadustat only)	.xx (.xx, .xx)	.xx	XXX	.xxx	.xxxx
PMM –Baseline Carried Forward (Both Groups)	.xx (.xx, .xx)	.xx	xxx	.xxx	.xxxx

* Maximum of Degree of Freedom from each individual ANCOVA. The actual Degrees of Freedom in PMM will be calculated using

$$\overline{U} = \frac{1}{m} \sum_{j=1}^{m} U_j.$$

between-imputation variance and

 $\overline{U} = \frac{1}{m} \sum_{j=1}^{m} U_j.$ with U the standard error associated with estimates, Rubin (1987).

** Set Hb to missing for Rescue Medication and 6 weeks afterwards (or 8 weeks if during the evaluation period)

11.1.3.1 MMRM Model

A mixed model of repeated measures (MMRM) will be used as one sensitivity analysis for the primary endpoint for US Submission (change from baseline in Hb from Week 28 to Week 52).

The model will contain terms for treatment arm, baseline measurement, visit (up to Week 52), visit by treatment interaction, and stratification factors except Screening Hb values (\leq 8 g/dL vs. > 8 g/dL). The primary efficacy analysis (for US [FDA]) will be based on the estimated difference between the two treatments overall mean effects throughout the evaluation period based on the MMRM model. Hb values under the influence of a rescue therapy will not be censored in the primary analysis.

Due to the large amount of visits to include in the model, data up to Week 52, the unstructured covariance pattern model will be applied first. If the algorithm for unstructured covariance pattern does not converge or the likelihood ratio test is not statistically significant then heterogeneous Toeplitz structure will be used. If this second model does not converge either then the (homogeneous) Toeplitz structure will be tried and finally compound symmetry as a covariance structure to achieve convergence. If none of them converge, first order autoregressive (AR (1)) as a covariance structure will be used to achieve convergence.

11.1.3.2 Pattern Mixture Model (PMM)

PMMs provide a general and flexible framework for sensitivity analyses that allows formulating assumptions regarding missing data in a transparent and clinically interpretable manner. This is expected to address the possibility of the data being missing not at random (MNAR). All factors mentioned in the primary analysis will be included in the PMM.

The following aspects of missing data, may affect the estimates.

- Timing and extent of missing data
- Assumed underlying mechanism for missing data

11.1.3.2.1 Timing and Extent of Missing Data

To assess the potential effect of missing data on the estimate of treatment effect, subjects will be classified as full data or missing data cases. Patterns of missing data will be based on non-missing hemoglobin before the end of the evaluation period.

- Full data cases are defined as subjects without any missing hemoglobin values for all scheduled assessments in the evaluation period.
- Missing data cases are defined as subjects with a missing hemoglobin on at least one scheduled Visit Week of the evaluation period. The missing data cases are further grouped into intermittent missing and monotone missing cases.

- o Intermittent missing hemoglobin cases are defined as subjects with a missing hemoglobin for at least one scheduled week of but not on consecutive scheduled weeks up to end of the evaluation period.
- o Monotone missing hemoglobin cases are defined as subjects who have consecutive scheduled Weeks with missing hemoglobin up to the end of evaluation period. A subject who is a Monotone missing case could have intermittent missing hemoglobin prior to the ending Week.

Subjects will be grouped as follows:

- Full data cases
- Intermittent missing data cases
- Monotone missing data cases

Should the incidence of Monotone missing data cases and intermittent missing data cases be relatively small, then those cases will be combined so that the groups are full data cases and missing data cases. The summary of missing pattern in first 52-week scheduled visit will be presented by treatment group in a table.

11.1.3.2.2 Assumptions on Missing Data Mechanism

In addition to the extent of missing data, the mechanism under which missing data occur may affect the estimate of the parameter of interest.

The potential impact of missing efficacy endpoints on the estimates of treatment effects will be assessed using alternative statistical models with different underlying assumptions on the missing data mechanism (missing not at random(MNAR)) (Little and Rubin, 1987).

A pattern-mixture model using a treatment-based multiple imputation method (Ratitch et al, 2011) will be used for a sensitivity analysis to explore the robustness of the ANCOVA results for the primary efficacy results.

11.1.3.2.3 PMM -Last Mean Carried Forward

A pattern-mixture model using a last mean carried forward multiple imputation method (Carpenter et al, 2013) will be used as another sensitivity analysis to explore the robustness of the ANCOVA results for the primary efficacy variables. Using this method, missing data after ending Week will be imputed based on the last non-missing mean from its own treatment group.

The steps to implement this sensitivity analysis are as follows. Parameters below refer to the parameters of the multivariate normal distribution for baseline and post baseline Hb measurement.

1. Create posterior distribution of parameters: Separately for each treatment group, take all patients observed data and assuming MAR to fit a multivariate normal distribution with unstructured mean (i.e. a separate mean for each of the baseline plus post-baseline

scheduled weeks and unstructured variance covariance matrix using a Bayesian approach with an improper prior for the mean and an uninformative Jereys' prior for the variance-covariance matrix (Schafer, 1997, p. 155).

- 2. Draw parameters: Separately for each treatment group, draw variance-covariance matrix from the posterior distribution for the parameters using seed 453628. The mean Vector would be set to the marginal mean for their randomized treatment arm at their last non-missing measurement.
- 3. Build joint distribution of missing data and observed data: For each subject with missing data, using the draws for the parameter to build the joint distribution of their observed and missing data.
- 4. Construct conditional distribution of missing data give observed data: For each patient with missing data, use their joint distribution in previous step to construct their conditional distribution of missing given observed outcome data. Sample their missing data from this conditional distribution, to create a "completed" data set, using seed 732545.

Repeat the above steps for 200 times and resulting in 200 imputed data sets. Then fit ANCOVA model for each imputation data set, and combine the resulting parameter estimates and standard errors using Rubin's rules (Rubin, 1987) for final inference.

11.1.3.2.4 PMM –Baseline Carried Forward (Roxadustat Only and Both Groups)

The analysis is the same as PMM – Last Mean Carried Forward except imputing the missing data. The imputation data will be generated similarly as last mean carried forward method described above but instead of using post-baseline observed data, only baseline data will be used. The similar analyses will be conduct in two scenarios.

- The baseline carried forward imputation will be performed for the roxadustat treatment group only, while for active control group, the imputation data will be generated using the last mean carried forward described above.
- The baseline carried forward imputation will be performed for the both treatment groups.

Similarly, the Rubin's method will be then used to combine the estimates and the differences between the least square mean differences between the two treatment groups from each of the ANCOVA analysis. This sensitivity analysis will be performed for U.S. primary endpoints only.

11.1.3.3 Logistic Regression

The primary analysis for Ex-US endpoint will also be repeated using logistic regression for PPS population. In addition to the stratification factors except Screening Hb values ($\leq 8 \text{ g/dL vs.} > 8 \text{ g/dL}$) and treatment group, and baseline Hb will be included as continuous covariates. The odds ratio for roxadustat versus placebo and its 95% confidence interval will be provided.

This model will also be repeated using logistic regression and adjusting by sex and age, in addition to the factors mentioned above.

11.1.3.4 Subgroup Analysis

The primary analysis of the US primary endpoint may be repeated separately by sex, age group, geographic region, baseline Hb categories, baseline CRP, baseline iron status, and cardiovascular/cerebrovascular/thromboembolic medical history on ITT Population. The subgroup analysis of the Ex-US primary endpoint may be performed on PPS for non-inferiority and FAS for superiority.

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11.2 ANALYSIS OF SECONDARY ENDPOINTS

The secondary endpoints are for both U.S. and Ex-U.S. submission unless otherwise specified. Once the primary hypothesis has been rejected for the primary endpoint, the secondary endpoints in the order that was specified in section 4.3 will be tested using a fixed sequence testing procedure, in order to maintain the overall two-sided type I error of 0.05. If p-value from a test is < 0.05, the claim of superiority or non-inferiority will be considered successful and the test will progress to the next comparison in sequence as follows.

Table 5 Key Secondary Endpoints Fixed Sequence Testing Procedure

Test	Variable	Comparison		
1	Proportion of subjects who achieve an Hb response at two consecutive visits during the first 24 weeks of treatment, (U.S.). or the mean Hb change from baseline to the average level during the Evaluation Period, defined as Week 28 until Week 52 for Ex-U.S	Non-inferiority of roxadustat versus EPO. The non-inferiority margin for the difference of responder analysis between groups is 0.15 The non-inferiority margin for the difference of average of Change in Hb values between groups is -0.75 g/dL.		
2	LDL cholesterol change from BL to the average of weeks 12 to 24.	Superiority of roxadustat versus EPO		
3	Mean change from baseline in Hb levels between Weeks 18 to 24 in patients whose baseline CRP> ULN:	The non-inferiority with margin of - 0.75 of roxadustat versus EPO		
4	Monthly IV iron (mg) use per subject during weeks 28 to 52.	Superiority of roxadustat versus EPO		
45	Time to first RBC transfusion during the treatment.	Non-inferiority of roxadustat versus EPO with Non-inferiority margin of 1.8		
5	Change from BL to the average MAP of weeks 8 to 12	Superiority of roxadustat versus EPO		
6	Time to first exacerbation of hypertension (defined as [systolic BP≥170 mmHg AND systolic BP increase from BL ≥20 mmHg] or [diastolic BP≥110 mmHg AND diastolic BP increase from BL≥15 mmHg]) during weeks 28 to 52	Superiority of roxadustat versus EPO & Non-inferiority with margin of 1.8		

11.2.1 Primary Analysis of Secondary Endpoints

The primary analysis for the secondary endpoints will be based on the PPS for the non-inferiority tests and FAS for the superiority tests for Ex-U.S. and FAS for U.S.

11.2.1.1 Hb

The first secondary efficacy endpoint for the US submission and the Ex-US submission will be the primary efficacy endpoint for the Ex-US submission and the US submission, respectively. The Ex-US secondary efficacy endpoint will use MMRM model described in 11.1.3.1. The US first secondary efficacy endpoints will use the same statistical analysis methodology for the primary efficacy endpoint for Ex-US.

11.2.1.2 Mean change from baseline in LDL cholesterol averaged over Weeks 12-24

The mean change from baseline in LDL cholesterol averaged over Weeks 12-24 will be compared between the 2 treatment groups using the MMRM model with baseline LDL cholesterol as a covariate, treatment group, visit, interaction of visit and treatment group, and the above-mentioned 4 stratification factors as fixed effects. The same strategy as that used in MMRM for Hb will be used to choose variance covariance structure. Data up to visit of Week 52 will be included in the model. The estimates for difference of LDL Cholesterol averaged over Weeks 12 to 24 between the two treatment groups will be generated from an estimate statement from Visit Week 12 to 24. Superiority will be declared if the upper bound of the 2-sided 95% confidence interval of the difference between roxadustat and Epoetin alfa (roxadustat - epoetin alfa) is less than 0.

11.2.1.3 Mean change from baseline in Hb levels between Weeks 18 to 24 in patients whose baseline CRP> ULN

Change from baseline in Hemoglobin from baseline to the average level during the Week 18 to 24 will be analyzed using the ANCOVA MI as the primary endpoints. Both Non-inferiority of roxadustat vs. Epoetin and superiority will be tested. The non-inferiority margin is fixed as a difference of -0.75.

11.2.1.4 Average monthly IV iron use during 28 to 52Weeks

The average monthly IV iron use during the treatment period will be calculated for monthly intervals. The treatment period will be divided in periods of 28 days and for each of these periods the monthly mean of IV iron will be used using the following formula:

Monthly iron use for each subject = Total IV iron in mg / [(last visit date – first drug date +1)/ 28]

The average monthly iron use will be compared between the 2 treatment groups using an ANCOVA model adjust for baseline iron replete, treatment group and above-mentioned stratification factors as fixed effects. Superiority will be declared if the lower bound of the 2-

sided 95% confidence interval of the difference between Epoetin alfa and roxadustat exceeds 0.

11.2.1.5 Mean change in mean arterial pressure (MAP) averaged over Weeks 8-12

Mean Arterial Pressure (MAP) will be calculated for each subject using the following formula: MAP = (2/3) * DBP + (1/3) * SBP.

Mean change from baseline in MAP will be analyzed and compared between the 2 treatment groups using an MMRM model with baseline MAP as a covariate, treatment group, visit, interaction of visit and treatment group, and above-mentioned stratification factors as fixed effects. The same strategy as that used in MMRM for Hb will be used to choose variance covariance structure. Data up to visit of Week 52 will be included in the model. The estimates for difference of MAP averaged over Weeks 8 to 12 between the two treatment groups will be generated from an estimate statement from Visit Week 8 to 12. Non-inferiority margin for the difference between groups is 1mmHg. Superiority will be declared if the upper bound of the 2-sided 95% confidence interval of the difference between roxadustat and ESA (roxadustat – ESA) is below 0.

11.2.1.6 Time to first exacerbation of hypertension over Week 28 to 52

Subject with exacerbation of hypertension is defined as meeting the following criterion:

Increase in blood pressure: An increase from baseline of ≥ 20 mm Hg systolic BP and sBP ≥ 170 mmHg or an increase from baseline of ≥ 15 mm Hg diastolic BP and dBP ≥ 100 mmHg. Increases from baseline in blood pressure are considered as confirmed by taking the mean of triplicates.

An exacerbation of hypertension is defined as an increase from baseline of \geq 20 mm Hg systolic BP and sBP >170 mmHg or an increase from baseline of \geq 15 mm Hg diastolic BP and dBP >100 mmHg).

Time to an exacerbation of hypertension in blood pressure will be analyzed and compared between the 2 treatment groups using the Cox Proportional Hazards model adjusting for baseline stratification factors. Both Non-inferiority and Superiority of roxadustat vs. ESA will be tested. The Non-inferiority margin for the difference between groups is 1.3 and the superiority margin for the difference between groups is 1. Subjects will be censored at the time of the last available blood pressure if an increase in blood pressure does not occur.

11.3 ADDITIONAL EFFICACY ANALYSES

The additional efficacy endpoints stated in section 4.3 will be analyzed using both the FAS.

11.3.1 Hb Correction and Maintenance

11.3.1.1 Time to achieve the first hemoglobin (Hb) response

Hemoglobin response is defined as the primary endpoint for the Ex-US submission and the first secondary endpoint for the US submission. It will be analyzed and compared between the 2 treatment groups using the Cox Proportional Hazards model adjusting for the above-

mentioned stratification factors. Non-inferiority of roxadustat vs. ESA will be tested. Non-inferiority will be declared if the upper bound of the 2-sided 95% confidence interval of the hazard ratio is less than 1.3. Subjects will be non-responder if the subject drop out the study early.

11.3.1.2 Hemoglobin Maintenance

Hemoglobin maintenance at Weeks 28-36 will be assessed by the mean change in Hb averaged over 8 weeks of treatment at Weeks 28-36 without rescue therapy within 6 weeks prior to and during this 8-week evaluation period.

The Hb values will be used on the central laboratory values. The Weeks will be defined using the visit window defined in Appendix 1.

The mean change in Hb will be analyzed using a MMRM model described in 11.1.3.1.

11.3.1.3 Hemoglobin Long-Term Maintenance

Hemoglobin long-term maintenance will be assessed by the mean change in Hb averaged over 8 weeks of treatment at Weeks 44-52 without rescue therapy within 6 weeks prior to and during this 8-week evaluation period. The mean change in Hb will be analyzed using the MMRM model described in 11.1.3.1

The mean change in Hb averaged over 8 weeks of treatment at Weeks 96-104 will be analyzed using the MI analyses as the one for the primary efficacy endpoint of US-submission.

Hemoglobin long-term maintenance will also be assessed by % patients with average Hb level >= 10 g/dL during weeks 28-36; 44-52; 68-76, 96-104, etc.

To evaluate Hb maintenance by other dosing frequencies, the following summary will be provided for the subgroups of subjects treated on BIW or QW (including any frequency <QW) for longer than 8 weeks (i.e., >=56 days):

- Average Hb values over time for every 4-8 weeks after the initiation of BIW or QW
- Average weekly dose over time for every 4-8 weeks after the initiation of BIW or QW

11.3.1.4 Hb Correction

Hb correction will be assessed using the following endpoints:

- Change in Hb at each of the selected post-dosing time points (see Table 4). Mean change in Hb at each of post-doing time points will be presented for the 2 treatment groups. The mean change will be compared between the 2 treatment groups using the MMRM model described in 11.1.3.1.
- Change in Hb averaged over 8 weeks of treatment at Weeks 28-36, without rescue therapy within 6 weeks prior to and during this 8-week evaluation period, in subjects who have reached an Hb ≥11 g/dL prior to Week 28. The same MMRM model will be

used to compare the mean change from baseline in Hb within this subgroup of subjects.

- Proportion of subjects with Hb within 10-12 g/dL in U.S. and 10-13 g/dL in Ex-U.S. averaged over Weeks 28-36, without rescue therapy within 6 weeks prior to and during this 8-week evaluation period. The proportion of subjects meeting the abovementioned criteria will be compared between the 2 treatment groups using logistic regression model adjusting for baseline Hb value as covariate with treatment group and baseline stratification factors except screening Hb values (≤ 8 g/dL vs. > 8 g/dL) as fixed effects.
 - Mean change in Hb from baseline to Week 28-36, from baseline to Week 28 to 52 in the subgroup of patients with baseline CRP>ULN.
 - Time to and minimum effective dose evaluation: Time to Hb≥11.0 g/dL and an increase by >=1 g/dL from baseline and the study drug dose will also be evaluated, with subgroup analysis by starting dose in the original protocol vs starting dose in the amended protocol.

Table 9 presents the analysis visits assigned for hemoglobin samples collection corresponding to the range of treatment days (window) during which an actual visit may have occurred. All scheduled and unscheduled hemoglobin samples that belong to each window will be taken into account.

11.3.2 Hospitalizations (including skilled nursing facility)

Hospitalizations are collected in the Hospitalization Records Form of the eCRF. For each subject, an entry will be recorded for each hospitalization. The days of hospitalization will be calculated as the sum of all hospitalizations durations in days (Date of discharge – Date of Admission + 1). In case of missing dates, the hospitalization duration will be assumed to be 5 days.

Only hospitalizations with admission dates that occur during the treatment period and up to 7 days after the last study medication date will be taken into account.

The following hospitalization-related data will be analyzed and compared between the 2 treatment groups:

- Time to first hospitalization up to Week 52- Proportion of subjects hospitalized. Time to first hospitalization or skilled nursing facility up to Week 52.
- Number of days of hospitalizations
- Number of days of medical-facility
- Number of days of hospitalizations per patient-exposure year (PEY).
- Number of days in hospital or skilled nursing facility per patient-year exposure (PEY)
- Number of days of medical-facility per subject-exposure year (PEY).

• Number of days on treatment out of hospital and skilled nursing facility up to Week 52, 7 days after Last Dose. The days will be compared between the 2 treatment groups using ANCOVA model with baseline Hb and the baseline stratification factors.

Note: Elective procedures may be excluded from analyses by using only hospitalization due to AE.

The time to hospitalization event will be compared between the two treatment groups using cox model including baseline stratification factors. The proportion of subjects hospitalized will be compared between the 2 treatment groups using logistic regression model and stratified by the baseline stratification factors. The mean number of days of hospitalization will be analyzed and compared between the 2 treatment groups using the Mantel-Haenszel mean score test adjusting for stratification factors.

11.3.3 Missed Dialysis Sessions

Missed dialysis sessions are collected in the Dialysis Modality Form of the eCRF. For each subject, an entry will be recorded for missing dialysis. The number of missing dialysis will be summarized by treatment group.

The following missing dialysis-related data will be analyzed and compared between the 2 treatment groups:

- Occurrence (number) of missed dialysis sessions. The number of missed dialysis sessions for each subject will be collected. The mean number of missed dialysis sessions will be analyzed and compared between the 2 treatment groups using Mantel-Haenszel mean score test adjusting for stratification factors.
- Proportion of subjects with missed dialysis sessions. The proportion of subjects missed dialysis sessions will be compared between the 2 treatment groups using CMH model and stratified by the baseline stratification factors.
- Number of days of missed dialysis sessions per patient-exposure year (PEY). The number of days of missed dialysis sessions for each subject will be calculated (# of missed dialysis/weekly prescribed dialysis frequency* 7), where weekly prescribed dialysis is TIW in this study. The mean number of days of missed dialysis sessions will be analyzed and compared between the 2 treatment groups using the Mantel-Haenszel mean score test adjusting for stratification factors.

11.3.4 Rescue Therapy Use

11.3.4.1 Blood Transfusion

For a subject receiving RBC transfusion, the Time at Risk (time up to first RBC transfusion) will be calculated (in years) as:

(First RBCtransfusion date – First dose date of study medication + 1) / 365.25

For a subject not receiving transfusion, the Time at Risk (time until they get censored) is calculated as:

(Date of last study medication – First dose date of study medication + 1) / 365.25

The blood transfusion form of the eCRF in the cumulative visit will be used to derive the number of RBC packs. The number of RBC units is collected in this form. For transfusions where the number of units is not given but the volume transfused is given, the number of units will be estimated by dividing the volume transfused by 250 mL (for transfusion of packed cells) or by dividing the volume transfused by 500 mL (for transfusion of whole blood).

The total number of RBC units/packs during the treatment period is calculated for each subject by the sum of the transfused units between the Analysis Date of First Dose and up to the Analysis Date of Last Dose. The following 2 endpoints will be analyzed:

- Proportion of subjects who receive RBC transfusions. The proportion of subjects who received RBC transfusion will be compared between the 2 treatments using logistic regression model adjusting for baseline stratification factors.
- Number of RBC packs per patient-month exposure to study medication. The mean number of RBC packs will be compared between the 2 treatment groups using ANCOVA model with baseline hemoglobin as covariate and treatment and stratification factors as fixed effect.

11.3.4.2 ESA Usage as Rescue Therapy for roxadustat-treated Subjects

For roxadustat-treated subjects, ESA, as rescue therapy will be recorded in the ESA log of the eCRF. The total number of ESA-week dose per subject will be calculated.

For each entry that meets the criteria below the ESA-week will be calculated as follows:

- o If drug is epoetin alfa, epoetin beta, or an epoetin biosimilar (ATC code: B03XA01), then ESA-Weeks = (stop date start date + 1) / 7;
- O If drug is darbepoetin SQ or IV dose (ATC code: B03XA02), then ESA-Weeks = 2 x (stop date start date + 1) / 7;
- o If drug is Mircera IV or SQ dose (ATC code: B03XA03), then ESA-Weeks = $4 \times (\text{stop date} \text{start date} + 1) / 7$;
- o If drug is peginesatide dose IV or SQ (ATC cod: B03XA04), then ESA-Weeks = 4 x (stop date start date + 1) / 7.

The total number of ESA-week during the treatment period is calculated for each subject by the sum of the ESA-week between the analysis date of First dose and the analysis date of Last dose.

11.3.4.3 Average Monthly IV iron use in 2nd and 3rd year of treatment

The same analysis of 11.2.1.4 will be perform for the above endpoint.

11.3.5 Changes in Cholesterol Levels

- Change at each of the selected treatment time points in:
 - o total cholesterol,

- o low-density lipoprotein/high-density lipoprotein ratio,
- o non-HDL cholesterol.

The mean change in these 3 endpoints at each post-dosing time point will be analyzed and compared between the 2 treatment groups using the MMRM model with baseline value as a covariate, treatment, visit and interaction of treatment and visit and stratification factors as fixed effects. The same strategy as that used in MMRM in Section 11.1.3.1 will be used to choose variance covariance. Data up to visit of Week 52 will be included in the analyses.

• Proportion of subjects achieving LDL target of <100 mg/dL averaged over Weeks 12-24 of treatment. The proportion of subjects achieving LDL target will be compared between the 2 treatment groups using logistic regression model adjusting for baseline LDL value and baseline stratification factors as fixed effects.

11.3.6 Blood Pressure Effect

- Proportion of subjects achieving blood pressure treatment goal in ESRD subjects (pre dialysis systolic BP <140 mmHg systolic and diastolic BP<90 mmHg) averaged over Weeks 12-28. The proportion of subjects achieving blood pressure goal will be compared between the 2 treatment groups using logistic regression model adjusting for baseline pre dialysis systolic and pre dialysis diastox1lic blood pressures as covariates and baseline stratification factors as fixed effects.
- Mean change in mean arterial pressure (MAP) averaged over Weeks 20-28

The same analysis as 11.2.1.5 will be performed for the above endpoint.

11.3.7 Vascular Access Thrombosis

- Time to a treatment-emergent AE of vascular access thrombosis
- Proportion subjects with a treatment-emergent AE of vascular access thrombosis

11.3.8 Health Related Quality of Life (HRQoL) and EQ-5D-5L Benefits of Anemia Therapy

The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) is a multi-purpose, short-form health survey with 36 questions (see appendix 2). It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. Accordingly, the SF-36 has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments. The SF-36 contains 36 items that measure eight dimensions: (1) physical functioning (PF); (2) role limitations due to physical health problems (RP); (3) bodily pain (BP); (4) social functioning (SF); (5) general health perceptions (GH); (6) role limitations due to emotional problems (RE); (7) vitality, energy or fatigue (VT); and (8) mental health (MH).

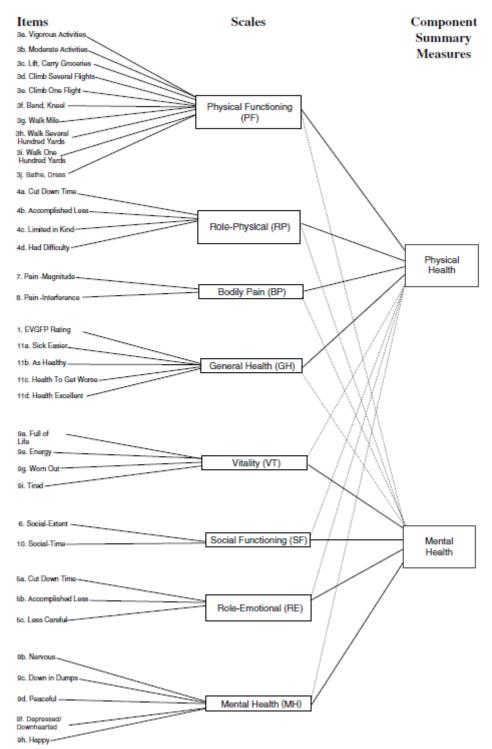
Table 6 Transformation of SF-36 items to a scale from 0 to 100

Question	Self-perceived health			
Question	0 (Poor)	100 (Better)		
1, 2, 6, 8, 9a, 9d, 9e, 9h, 11b, 11d	5	1		
3a to 3j	1	3		
4a to 4d, 5a to 5c, 9b, 9c, 9f, 9g, 9i, 10, 11a, 11c	1	5		
7	6	1		
Programming note: Once transformed – the items should each span the range 0 to				
100.	_	_		

Item scores for each dimension are coded, summed, and transformed to a scale from 0 to 100, with higher scores indicating better self-perceived health (See detail in 4). The transformed items are then averaged to give the subscales. The subscales are averaged to give the composite scores. The composite scores are averaged to give the overall score. The reliability and validity of the SF-36 is well documented in a variety of different patient groups, including patients with vascular diseases.

For each of the 8 dimensions, if less than 50% of the items which constitute that dimension are missing, the dimension score will be calculated by the mean of the available non-missing items. The physical health composite summary and mental health composite summary will only be calculated if a score has been calculated for all 4 dimensions that constitute the composite summary.

Figure 1. SF-36 Model



The mean change from baseline at weeks 12, 36, and 52 weeks will be computed for each treatment group. A paired t-test will be used to assess within treatment effect. Between treatment difference will be assessed using the MMRM model with baseline sub-score as a covariate, and treatment group, visit, interaction of treatment and visit, and stratification factors as fixed effects. The same strategy as that used in MMRM in Section 11.1.3.1 will be used to choose variance covariance. Data up to visit of Week 52 will be included in the analyses. Non-inferiority of roxadustat vs. ESA will be tested. The non-inferiority margin is fixed as a difference of 2 points.

HRQoL benefit will also be assessed using SF-36 vitality and physical functioning subscales. Mean change in following endpoints at above-mentioned time points will be analyzed and compared between the 2 treatment groups using MMRM using the baseline value as a covariate, treatment group, visit, the interaction of treatment and visit, adjusting for the stratification factors. The same strategy as that used in MMRM for Hb will be used to choose variance covariance structure. Other than below endpoints for exploratory analyses, other QoL variables may be performed

- Vitality Subscale of SF-36: In FAS subjects with baseline Vitality Sub-score below 50.
- Physical Component Scores of SF-36:
 - o In FAS subjects with baseline *physical component scores* below 40.
 - o In all FAS subjects.
- Anemia Subscale ("Additional Concerns") of Functional Assessment of Cancer Therapy-Anemia (FACT-An) Scores:
 - o In FAS subjects with baseline subscale scores below 55 (generally associated with fatigue).
 - o In all FAS subjects.
- Total FACT-An Scores:
 - o In FAS subjects with baseline FACT-An scores below 135
 - o In all FAS subjects.
- EQ-5D-5L Scores: In all FAS subjects.

11.3.9 Hepcidin, Iron, and HbA1c

The mean change from baseline in the following endpoints will be analyzed using the MMRM model with baseline value as a covariate and treatment group and stratification factors as fixed effects with the same strategy as that used in MMRM in Section 11.1.3.1 will be used to choose variance covariance and data up to visit of Week 52 will be included in the analyses:

• Change from baseline in serum hepcidin at each of the selected time points (e.g., Weeks 4, 12, 20, 44 and every 8 weeks onwards)

- Change from baseline in CHr at each of the selected time points (e.g., Weeks 4, 8, 12, 20, 28, and every 8 weeks onwards)
- Change from baseline in serum ferritin at each of the selected time points, total and sub-grouped by baseline values of <100 ng/mL, 100 to <400 ng/mL and >=400 ng/mL.
- Change from baseline in TSAT at each of the selected time points, total and subgrouped by baseline values of <20%, 20% to <40%, and >=40%.
- Serum iron at each of the time points tested
- CHr at each timepoint tested (Weeks 4, 8, 12, 20, 28, 36, every 8 weeks onwards)
- Proportion of patients with CHr > ULN at each timepoint tested: Weeks 4, 8, 12, 20, 28, 36, every 8 weeks onwards)
- Change in HbA1c level at each of the selected time points in subjects without history of diabetes, in subjects with history of diabetes.

12 SAFETY ANALYSES

The safety analysis will be performed using the Safety Population. Safety parameters include adverse events, laboratory parameters, vital signs, ECG parameters, and physical examinations.

Safety interpretation will also be made based on analyses of composite endpoints derived from adjudicated events pooled across multiple studies in the roxadustat Phase 3 program per pooled statistical analysis plan (PSAP) on dialysis studies in the roxadustat program.

For each safety parameter, the last assessment made prior to the first dose of study medication will be used as the BL for all analyses of that safety parameter.

12.1 ADVERSE EVENTS

Adverse events will be coded using the latest MedDRA version.

12.1.1 Proportion of Subjects with TEAE

An AE (classified by preferred term) started during the treatment period will be considered a treatment-emergent adverse event (TEAE) if it was not present prior to the first dose of study medication, or it was present prior to the first dose of study medication but increased in severity during the treatment period up to 7 days after last dose of study drug or until the administration of another anemia drug (other than the randomized treatment). An AE that occurs more than 7 days after the last dose of study medication or after the administration of another anemia drug (other than the randomized treatment) will not be counted as a TEAE.

The number and percentage of subjects reporting TEAEs in each treatment group will be tabulated separately by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and relationship to study medication. If more than one event occurs with the same preferred term for the same patient, the patient will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the study medication.

The distribution of TEAEs by severity and relationship to study medication will be summarized by treatment group.

The incidence of common (\geq 5% of subjects in any treatment group) TEAEs, treatment-emergent serious AEs (TESAE), and AEs leading to discontinuation of study medication will be summarized by preferred term and treatment group, sorted in decreasing overall (across treatments) frequency. In addition, the incidence of death and fatal SAEs (i.e., events that caused death) and incidence rate per PEY will be summarized separately by treatment group and preferred term.

Listings will be presented of subjects with serious adverse events (SAEs), subjects with adverse events leading to discontinuation, and subjects who died.

Temporal profile of TEAEs of special interest may also be plotted by treatment group showing the subjects in the y-axis and time to these TEAEs in the x-axis (Appendix 8).

12.2 CLINICAL LABORATORY PARAMETERS

Descriptive statistics for laboratory values (in US conventional and SI units) and changes from baseline at each assessment time point will be presented by treatment group for the following laboratory parameters collected in the study including but are not limited to the following:

- Hematology: Hemoglobin, hematocrit, RBC count, MCV, MCH, MCHC, WBC count, WBC differential, platelet counts and Reticulocyte count;
- Chemistry: CPK, ALP, ALT, AST, total bilirubin, LDH, total protein, albumin, glucose, phosphate, uric acid, BUN, creatinine, sodium, and potassium; HbA1C;
- Serum iron, ferritin, TIBC, TSAT
- CHr
- Hepcidin
- CRP

Laboratory tests values are clinically significant (CS) if they meet either the low or high CS criteria. The number and percentage of subjects with post-baseline CS values will be tabulated by treatment group. The percentages are to be calculated relative to the number of subjects with available non-CS baseline values and at least one post-baseline assessment. The numerator is the total number of subjects with at least one post-baseline CS value. In addition, shift tables will be presented by treatment group and time point. The following 3 data listings will be presented by subject:

- A listing of lab values for all lab tests at all collected time points.
- A listing of subjects with post-baseline CS values will be provided including the baseline and post-baseline values.
- A listing of all AEs for subjects with CS laboratory values will also be provided.

12.3 VITAL SIGNS

Blood Pressures and Heart Rate baselines are defined as the mean of values obtained from the last 6 weeks of screening including Day 1 prior to the first dose. For subjects on hemodialysis, pre-dialysis vital signs will be used. For subjects on peritoneal dialysis, vital signs may be recorded at any time during the visit.

Descriptive statistics for vital signs (e.g., systolic and diastolic blood pressure, MAP, heart rate, and respiratory rate) and their changes from baseline at each visit and at the end of study will be presented by treatment group.

Vital sign values are potentially clinically significant (PCS) if they meet both the observed value criteria and the change from baseline criteria listed in Table 6 below. The number and percentage of subjects with post-baseline PCS values will be tabulated by treatment group. The percentages are to be calculated relative to the number of subjects with baseline and at least one post-baseline assessment. The numerator is the total number of subjects with at least one post-baseline PCS vital sign value. Shift tables may be presented. A supportive listing of subjects with post-baseline PCS values will be provided including the patient ID, study center, baseline, and post-baseline values. A listing of all AEs for subjects with PCS vital signs will also be provided.

Table 7. Criteria for Potentially Clinically Significant Vital Signs

Vital Sign	E1	Criteria*		
Parameter	Flag	Observed Value	Change from Baseline	
Systolic Blood	High	≥ 170	Increase of ≥ 20	
Pressure (mmHg)	Low	≤ 90	Decrease of ≥ 20	
Diastolic Blood	High	≥ 100	Increase of ≥ 15	
Pressure (mmHg)	Low	≤ 50	Decrease of ≥ 15	
Pulse Rate	High	≥ 120	Increase of ≥ 20	
(bpm)	Low	≤ 50	Decrease of ≥ 20	
Weight	High	-	Increase of ≥ 10%	
(kg)	Low	-	Decrease of ≥ 10%	

Additional analyses include but are not limited to

- Subgroup analyses of patients without any change in BP meds during treatment period
- Proportion of subjects meeting NKF BP target: within sBP 120-140 mmHg/dBP 70-90 mmHg at baseline, during treatment, and 4 weeks post treatment

^{*}A post-baseline pre-dialysis or post-dialysis value is considered as a PCS value if it meets both criteria for observed value and change from pre-dialysis or post-dialysis baseline.

12.4 ELECTROCARDIOGRAM (ECG)

Descriptive statistics for ECG parameters (e.g., Heart Rate, PR interval, QRS interval, QT interval, and QTc interval) at baseline and changes from baseline at each assessment time point will be presented by treatment group. QTc interval will be calculated using both Bazett (QTcB = QT/(RR) $^{1/2}$) and Fridericia (QTcF = QT/(RR) $^{1/3}$) corrections; and if RR is not available, it will be replaced with 60/HR in the correction formula.

A plot for each parameter of mean (+/- 95% CI) versus visit will be produced by treatment group (roxadustat vs. ESA).

ECG parameters values are potentially clinically significant (PCS) if they meet or exceed the upper limit values listed in Table 8 below. The number and percentage of subjects with post-baseline PCS values will be tabulated by treatment group. The percentages are to be calculated relative to the number of subjects with available non-PCS baseline and at least one post-baseline assessment. The numerator is the total number of subjects with at least one post-baseline PCS ECG value. Shift tables may be presented. A listing for all subjects with post-baseline PCS value will be provided including the patient ID, study center, baseline, and post-baseline PCS values.

In addition, a listing of all TEAEs for subjects with PCS ECG values and a listing of subjects with post-baseline significant ECG abnormalities as reported by the investigators will also be provided.

Table 8. Criteria for Potentially Clinically Significant ECG

ECG Parameter	Unit	Higher Limit
QRS interval	Msec	≥ 150
PR interval	Msec	≥ 250
QTc interval	Msec	> 500; Change from baseline > 60

12.5 OTHER SAFETY ANALYSES

A separate meta-analysis SAP for pre-specified, adjudicated composite safety endpoints to assess Cardiovascular, cerebrovascular and thrombo-embolic Events will be developed to complement this study specific SAP.

13 ADDITIONAL AND SUBGROUP ANALYSES

The analysis of the primary endpoints of US and EU, and Hb change from baseline to the average level during Week 18 to 24 may be performed separately by sex, age group, baseline iron replete status, baseline CRP group (<= ULN vs > ULN), and baseline stratification factors.

14 INTERIM ANALYSIS

Safety data and dosing decisions will be monitored on an ongoing basis. Additional ongoing review of safety data will be conducted by an independent DSMB (see protocol Section 3.7).

15 REFERENCES

- ICH Harmonized Tripartite Guideline E3. Structure and Content of Clinical Study Reports, November 1995. (www.ich.org; Guidelines; "Efficacy" Topics)
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11/23/2020

16 APPENDIX

16.1 APPENDIX 1: SCHEDULE OF ASSESSMENTS

Study Period:	Scr	eenin	g			Treatment			Follow-up
Visit / Week:	Ţ	Up to Weeks		Day 1 (Wk 0)	Weekly (Wks 1 to 4) ± 2 days	Every 2 Weeks (Wks 6 to 24) ± 2 days	Every 4 Weeks (Wks 28 to EOT) ± 3 days ^b	EOT or ET ¹ ± 3 days	EOS
	1	2	3						
Written informed consent	X								
Eligibility criteria	X			X					
Demographics and medical history	X								
Physical examination	X			X		Wks 12 °, 24 °	Wks 36 °, Q12wk °, d	X	X ^c
Height, weight	X			X e			Wk 24 and every 24 wks ^e		
Blood pressure, heart rate, respiratory rate, temperature ^f	X	X	X	X	X	X	X	X	X
Hemoglobin		X	X			X g	X ^g		
CBC with WBC differential	X			X	X	Wks 8. 12, 20	Wk 28, Q8wk	X	X
Serum chemistry	X			X	Wk 2	Wks 8,12, 20	Wk 28, Q8wk	X	X
LFTs, CPK					Wk 2	Wks 6, 16			
Lipid panel (whenever fasting possible)	X			X	Wk 4	Wks 8, 12, 24	Wks 32, 40, 48, 60, Q24wk	X	X
Serum iron, ferritin, TIBC, TSAT	X			X	Wk 4	Wks 8, 12, 20	Wk 28, Q8wk	X	X
CHr	X			X	Wk 4	Wks 8, 12, 20	Wk 28, Q8wk	X	X
HbA1c	X			X		Wk 12	Wks 28, 44, 60 Q16wk d	X	X
Vitamin B ₁₂ , folate	X								
HIV ELISA, HBsAg, anti-HCV Ab	X								
Serum hCG pregnancy test	X h					Wks 12, 24	Wk 36, then Q12wks	X	X
Reticulocyte count				X	Wks 1, 2	Wks 8, 20	Wk 44, Q24wk	X	X
Special laboratory analytes (hepcidin, hs-CRP)				X	Wk 4	Wks 12, 20	Wk 44, Q24wk	X	X
Optional archival serum/plasma samples				X	Wk 4	Wks 12, 20	Wk 44, Q24wk ^d	X	X
HemoCue [®] assessment				X	X	X	X		
Quality-of-life questionnaires				X		Wk 12	Wks 36, 52 d	X	
12-lead ECG				X			Wk 24 and every 24 wks	X	
Renal ultrasound i		Х							
Dose adjustment j					X	X	X		
Adverse event recording	X	X	X	X	X	X	X	X	X
Concomitant medication recording	X	X	X	X	X	X	X	X	X
Procedure and nondrug therapy recording	X	X	X	X	X	X	X	X	X
Study drug dispensing k				X	X ¹	X	X		

Footnotes on following page

Abbreviations:

Ab = antibody; BP = blood pressure; CBC = complete blood count; CHr = reticulocyte hemoglobin content; ELISA = enzyme-linked immunosorbent assay; EOT = End of Treatment; EOS = End of Study; ET = early termination; Hb = hemoglobin; HbA1c = glycated hemoglobin A1c; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HD = hemodialysis; HIV = human immunodeficiency virus; HR = heart rate; HRQoL = health-related quality of life questionnaire; HS-CRP = high-sensitivity C reactive protein; ICF = informed consent form; LFTs = liver function tests; PE = physical examination; RBC = red blood cell; RR = respiratory rate; SmPC = summary of product characteristics; TIBC = total iron binding capacity; TSAT = transferrin saturation; TX = treatment; WBC = white blood cells; Wk(s) = week(s); X = mandatory test/assessment.

- a Screening Hb values must be obtained at least 4 days apart.
- b Treatment duration is variable for each subject. All subjects will remain in the study treatment until up to 3 years s after the last subject randomized.
- c Targeted PE only (e.g., respiratory and cardiovascular).
- d If the indicated assessments fall on a study treatment visit that is within two weeks of the planned EOT visit then these specified assessments can be postponed until the EOT visit.
- e Weight only (HD subjects: use dry weight).
- f Perform HR and BP at all week visits. Additional respiratory rate and temperature are measured at Day 1/Week 0 and EOT/ET.
- g Dedicated Hb sample for central lab should be collected during the visits where CBC is not collected.
- h Collect from female subjects of child bearing potential only.
- i A renal ultrasound examination will be performed during screening if no record of a renal imaging modality exists within 12 weeks prior to randomization.
- j Roxadustat subjects: Dose adjustments will be permitted from Week 4 onward, and every 4 weeks thereafter (except in extenuating circumstances) to correct and maintain subjects to a target Hb range. Please refer to dose adjustment rules as stated in **Error! Reference source not found.**
 - Epoetin alfa subjects: Dose adjustments for HD subjects receiving epoetin alfa will follow the country specific product labeling for dosing and dose adjustments (e.g., PI; SmPC). For PD subjects, local standard of care may be followed for dosing and dose adjustments.
- k All assessments should be done prior to first study drug administration.
- 1 Dispense every other week
- m Subjects who prematurely discontinue study treatment will complete the ET and EOS visits, and unless consent is withdrawn will continue to be followed for CV events of interest, vital status and hospitalizations until study closure. These subjects will be asked to return for study visits every 3 to 6 months, or be available via telephone.

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16.2 APPENDIX 2: DATA HANGLING CONVENTIONS

16.2.1 VISIT TIME WINDOW

Table 9 below presents the visits assigned for efficacy and safety analyses corresponding to the range of treatment days (window) during which an actual visit may have occurred.

Table 9. Analysis Visit Windows

Derived Visit	Scheduled Visit Day ^a	Window		
Baseline, Week 0	Day 1	Days ≤ 1		
Week 1	Day 7*(Week #)+1	[Day 2, 10]		
Weeks 2-3	Day 7*(Week #)+1	Days [Scheduled Day ± 3]		
Week 4	Day 7*(Week #)+1	[Scheduled Day -3, Scheduled Day +6]		
Weeks 4-22	Day 7*(Week #)+1	[Scheduled Day -7, Scheduled Day +6]		
Week 24	Day 7*(Week #)+1	[Scheduled Day -7, Scheduled Day +13]		
Week 24 to xx	Day 7*(Week#)+1	[Scheduled Day -14, Scheduled Day +13]		
ET	Earlier Termination, Match to a closest scheduled visit in protocol if patient had not been off drug for more than 7 days.			
ЕоТ	Last assessment between Day 2 and EOT visit day, match to a closest scheduled visit in protocol if patient had not been off drug for more than 7 days.			
EoS (FU-4Wk)	Final visit for the Study 15 – 31 days after the last dose (excluding long term follow-up for early termination)			

^a: Relative to the first study medication date. For example, Day 1 = the first dose date of study medication.

Analysis Visit windows, as depicted in Table 10 below, will be used for the quality of life efficacy study assessments:

Table 10: Analysis Visit Windows for QoL

CRF Visit	Target Day ^a	Analysis Visit Windows Actual Assessment Day	Analysis Visit
Day 1	Day 1	Day 1	Baseline
Week 12	Day 7 * (Week #) + 1	[Target Day -14, Target Day + 27]	Week 12
Week 36	Day 7 * (Week #) + 1	[Target Day – 28, Target Day +27]	Week 36
Week 52	Day 7 * (Week #) + 1	>=Target Day – 56, Target day + 83	Week 52
EOT Visit		Last assessment between Day 2 and EOT visit day, remapped to the closest next scheduled visit for HRQoL collection.	Week 12, 36, 52 and > 1 year

^a: Relative to Day 1 (first dose date of study medication)

Table 11. Analysis Visit Windows for Lipid Panel

Derived Visit	Scheduled Visit Day ^a	Window	
Baseline, Week 0	Day 1	Days 1	
Week 4	Day 7*(Week #)+1	[Day 2, 42]	
Week 8	Day 7*(Week #)+1	[Scheduled Day-14, Scheduled Day +13]	
Weeks 12	Day 7*(Week #)+1	[Scheduled Day -14, Scheduled Day +27]	
Week 24	Day 7*(Week #)+1	[Scheduled Day -28, Scheduled Day +27]	
Weeks 32-40	Day 7*(Week #)+1	[Scheduled Day -28, Scheduled Day +27]	
Week 48	Day 7*(Week #)+1 [Scheduled Day -28, Scheduled Day +		
Week 60	Day 7*(Week #)+1	[Scheduled Day -42, Scheduled Day +83]	
Week 84 to xx	Day 7*(Week#)+1 [Scheduled Day -84, Scheduled Day 83]		
ЕоТ	Last assessment between Day 2 and EOT visit day, match to a closest scheduled visit in protocol if patient had not been off drug for more than 7 days		

^a: Relative to Day 1 (first dose date of study medication)

Visit Day is calculated by (visit date - date of first study medication + 1). If a patient has ≥ 2 actual visits within the same window, the last visit with non-missing value will be used for analysis.

16.2.2 Repeated or Unscheduled Assessments of Safety Parameters

If a patient has repeated assessments prior to the start of study medication, then the results from the final assessment made prior to the start of study medication will be used as baseline. If end of study assessments are repeated or unscheduled, the last post-baseline assessment will be used as the end of study assessment for generating summary statistics. However, all post-baseline assessments will be used for PCS value determination and all assessments will be presented in the data listings.

16.2.3 Missing Date of Study Medication

When the last date of study medication during the study treatment phase is missing, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, then the last dispensation visit date during the treatment period will be used in the calculation of treatment duration.

16.2.4 Missing Severity Assessment for Adverse Events

If severity is missing for an AE started prior to the first study medication, then a severity of "Mild" will be assigned. If the severity is missing for an AE started on or after the first study medication dosing, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summary, while the actual missing values will be presented in data listings.

16.2.5 Missing Relationship to Study Drug for Adverse Events

If the relationship to the study medication is missing for an AE started after baseline, a causality of "Related" will be assigned. The imputed values for relationship to study medication will be used for incidence summary, while the actual values will be presented in data listings.

16.2.6 Missing Date Information for Adverse Events

The following imputation rules only apply to the case where the start date is incomplete (i.e., partial missing) for adverse events.

Incomplete Start Date

Missing day and month

- If the year is same as the year of first day on study medication, then the day and month
 of the start date of study medication will be assigned to the missing fields.
- If the year is not the same as the year of first day on study medication, then January 1 will be assigned to the missing fields.

Missing month only

Treat day as missing and replace both month and day according to the above procedure. *Missing day only*

If the month and year are same as the year and month of first day on study medication, then the start date of study medication will be assigned to the missing day.

If the month and year are not the same as the year and month of first day on study medication, then the first day of the month will be assigned to the missing day.

• Incomplete Stop Date

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If needed, the following imputation rules apply to the case where the end date is incomplete (i.e., partially missing) for adverse events. Other partial end date will not be imputed.

Missing day and month, or Missing month only

December 31 will be assigned to the missing fields.

Missing day only

The last day of the month will be assigned to the missing day.

Table 16.6-1 Imputation of the Analysis Adverse Event Start Date

Reported Date	Date of First Drug Intake	Analysis Date (Derived)
/MM/YYYY	DD/MM/YYYY	
/02/2008	14/02/2008	14/02/2008*
/02/2008	14/02/2007	01/02/2008
/02/2008	14/02/2009	01/02/2008
//YYYY	DD/MM/YYYY	
//2008	14/02/2008	14/02/2008
//2008	14/02/2007	01/01/2008
//2008	14/02/2009	01/01/2008
DD//		
/MM/		No imputation
/		

Table 16.6-2 Imputation of the Analysis Adverse Event Stop Date

Reported Date	Analysis Date (Derived) *	
/MM/YYYY	31/MM/YYYY or	
	30/MM/YYYY or	
	29/MM/YYYY or	
	28/MM/YYYY	
//YYYY	31/12/YYYY	
DD//, or		
/MM/, or	No imputation	
/		

^{*}Death has to be taken into consideration when calculating this.

16.2.7 Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, including rescue medications, incomplete (i.e., partial missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a patient, impute the start date first.

• Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing day and month

- If the year of the incomplete start date is the same as the year of the first dose date of study medication, then the day and month of the first dose date will be assigned to the missing fields.
- If the year of the incomplete start date is not the same as the year of the first dose date of study medication, then January 1 will be assigned to the missing fields.

Missing month only

Treat day as missing and replace both month and day according to the above procedure. *Missing day only*

- If the month and year of the incomplete start date are the same as the month and year of the first dose date of study medication, then the day of the first dose date will be assigned to the missing day.
- If the month and year of the incomplete start date are the same as the first dose date of study medication, then the first day of the month will be assigned to the missing day.

• Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields, if needed. If the last dose date of study medication is missing, impute it with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

Missing day and month

If the year of the incomplete stop date is the same as the year of the last dose date of study medication, then the day and month of the last dose date will be assigned to the missing fields.

If the year of the incomplete stop date is not the same as the year of the last dose date of study medication, then December 31 will be assigned to the missing fields.

Missing month only

Treat day as missing and replace both month and day according to the above procedure. *Missing day only*

If the month and year of the incomplete stop date are the same as the month and year of the last dose date of study medication, then the day of the last dose date will be assigned to the missing day.

If the month and year of the incomplete stop date are not the same as the month and year of the last dose date of double-blind study medication, then the first day of the month will be assigned to the missing day.

16.2.8 Missing Date Imputation for last dose date

Imputed last dose date = earliest date of (last drug dispense date + number of days of drug dispensed, date of death, date of EOT/EOS visit, and other dates as appropriate).

16.2.9 Character Values of Clinical Laboratory Parameters

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table due to, for example, that a character string is reported for a parameter of the numerical type, coded value needs to be appropriately determined and used in the statistical analyses. However, the actual values as reported in the database will be presented in data listings.

Table 12. Example for Coding of Special Character Values for Clinical Laboratory Parameters

Lab Test	Possible Lab Results (in SI unit)	Coded Value for Analysis
Urinalysis: Ketones	= OR > 8.0, >= 8.0, > 0	Positive
	<= 0, Negative	Negative
Urinalysis: pH	> 8.0, >= 8.0	8.0
	>= 8.5,	8.5
Urinalysis: Protein	= OR > 3.0, >=3.0, > 0	Positive
	<= 0	Negative

16.3 **APPENDIX 3: RANGES OF POTENTIALLY CLINICALLY** SIGNIFICANT LAB VALUES

Parameter	SI Unit	Lower Limit	Higher Limit			
CHEMISTRY						
Alanine Aminotransferase (ALT)	U/L		≥3 * ULN			
Alkaline Phosphatase	U/L		≥3 * ULN			
Aspartate Aminotransferase (AST)	U/L		≥3 * ULN			
GGT	U/L		≥3 * ULN			
Calcium	mmol/L	<0.8*LLN	>1.2 * ULN			
Creatinine	μmol/L		> 1.5x Baseline value			
Potassium	μmol/L	<0.75*LLN	>1.2 * UNL			
Sodium	mmol/L	<0.9*LNL	>1.1 * UNL			
Total Bilirubin	μmol/L		>1.5 * UNL			
Total Protein	μmol/L	<0.9*LNL	>1.1 * UNL			
Urea (BUN)	mmol/L		>1.5X Baseline value			
HEMATOLOGY						
Neutrophils	10 ⁹ /L	≤1				
Platelet Count	10 ⁹ /L	≤ 100	≥700			
White Blood Cell Count	10 ⁹ /L	≤2.5	≥15			
White Blood Cell Count $ 10^9/L \le 2.5 $ ≥ 15 LLN: Lower limit of normal, value provided by the laboratory						

ULN: Upper limit of normal, value provided by the laboratory

16.4 APPENDIX 4: SF-36 V2

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:



 Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
V				
1	\square_2	<u></u> 3	4	5

SF-36 v2

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

		limited	Yes, limited a little	limited
а	<u>Vigorous activities</u> , such as running, lifting heavy objects, participating in strenuous sports	□1	🗀 2	🔲 3
b	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	□1	🗆 2	
С	Lifting or carrying groceries	□1	2	Дз
d	Climbing several flights of stairs	□1	🗀 2	Дз
e	Climbing one flight of stairs	□1		Дз
f	Bending, kneeling, or stooping	□1	2	,, <u>,</u> _3
g	Walking more than a mile	□1	🗀 2	□3
h	Walking several hundred yards	□1	2	<u> </u> 3
i	Walking one hundred yards	□1.,	🗆 2	Дз
j	Bathing or dressing yourself	□1	🗆 2	

SF-36 v2

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
		\blacksquare				
a	Cut down on the <u>amount of</u> <u>time</u> you spent on work or other activities	□1	D ₂	□₃	🗆 4	5
b	Accomplished less than you would like	□1	□₂	□з	□₄	5
С	Were limited in the <u>kind</u> of work or other activities	🗆 1 , ,	🗆 2	□з	□₄	5
d	Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort) •	□ ₁ ,.	🗆 2	□₃.,	🗆 4 . ,	5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

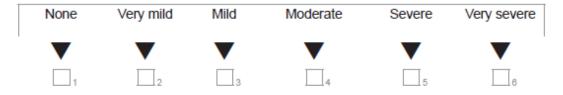
		All of the time	Most of the time	Some of the time	A little of the time	None of the time
	,	\blacksquare				\blacksquare
a	Cut down on the <u>amount of</u> <u>time</u> you spent on work or other activities	□1,,		🗆 з	🗆 4	5
b	Accomplished less than you would like	□1	□₂	🗆 3	🗆 4	5
С	Did work or other activities less carefully than usual	□1	□ ₂		4	5

SF-36 v2

6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
V		•	\blacksquare	•
1	_2	3	4	5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?



8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
V	lacksquare	lacksquare	•	lacksquare
1	2	3	4	5

SF-36 v2

9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>...

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	Did you feel full of life?	🗆 1 , ,	2	🗆 з . ,	🗆 4	5
ь	Have you been very nervous?	□1	D ₂	3	4	5
c	Have you felt so down in the dumps that nothing could cheer you up?	□1		3	4	5
d	Have you felt calm and peaceful?	🗆 1		3	4	5
е	Did you have a lot of energy?	,,, □1,,		🗆 з	🗀 4	5
f	Have you felt downhearted and low?	🗆 1	□2 ,.	□₃	□4	5
8	Did you feel worn out?	🗆 1		3	🗀 4	5
h	Have you been happy?	🗆 1		🗆 з	🗆 4	5
i	Did you feel tired?	🗆 1	□2	3	🗆 4	5
0	Ouring the <u>past 4 weeks,</u> he or emotional problems inte vith friends, relatives, etc.)	rfered wi				
	All of Most of the time		ome of e time	A little of the time		lone of ne time

SF-36 v2

11. How TRUE or FALSE is each of the following statements for you?

		Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a	I seem to get ill more easily than other people	□1	🗆 2	🗆 3	□4	5
b	I am as healthy as anybody I know	□1,.	□₂	🗆 3	□4 .	5
С	I expect my health to get worse	□1,,	□ ₂	🗆 3	4	5
d	My health is excellent	□₁	□₂	🗆 3	4	5

Thank you for completing these questions!

16.5 APPENDIX 5: FACT-AN (VERSION 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	PHYSICAL WELL-BEING	Not at all	A little bit	Some- what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4
	SOCIAL/FAMILY WELL-BEING	Not at all	A little	Some- what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section.					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-An (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some- what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4
	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some- what	Quite a bit	Very much
GF1	FUNCTIONAL WELL-BEING I am able to work (include work at home)				_,	
GF1 GF2		at all	bit	what	a bit	much
	I am able to work (include work at home)	at all	bit 1	what 2	a bit	much 4
GF2	I am able to work (include work at home)	at all	bit 1	what 2 2	a bit 3	much 4 4
GF2 GF3	I am able to work (include work at home) My work (include work at home) is fulfilling	at all 0 0 0	bit 1 1	what 2 2 2	a bit 3 3 3	4 4 4
GF2 GF3 GF4	I am able to work (include work at home) My work (include work at home) is fulfilling I am able to enjoy life I have accepted my illness	at all 0 0 0 0 0	bit 1 1 1 1	what 2 2 2 2	a bit 3 3 3 3	4 4 4 4

FACT-An (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some- what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An9	I feel lightheaded (dizzy)	0	1	2	3	4
An10	I get headaches	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
An11	I have pain in my chest	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
An13	I am motivated to do my usual activities	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

16.6 APPENDIX 6: JUSTIFICATION FOR THE NONINFERIORITY MARGIN OF 0.75 MG/DL

The **FDA** draft Guidance for Industry: Non-Inferiority Clinical Trials states that "the NI trial concept depends on how much is known about the size of the treatment effect the active comparator will have in the NI study compared to no treatment" and this effect "must be assumed, based on an analysis of past studies of the control".

Pursuant to this, we sought out studies that compared ESA therapies currently approved for use in the United States to placebo (or no therapy) in the treatment of anemia. Criteria to be considered relevant to estimate the potential treatment effect included:

- 1- Randomized trial design
- 2- Prospective follow up
- 3- Treatment groups which included epoetin-alfa (or other recombinant erythropoeitin derivatives) and either placebo or no treatment
- 4- Inclusion of treatment naïve adult patients with CKD or ESRD related anemia.
- 5- Post randomization monitoring of hemoglobin following randomization
- 6- Reporting either hemoglobin or hematocrit summary measures at baseline and during follow-up

Studies were identified through a search of the bibliographies peer-reviewed metaanalyses examining the effect of ESAs on outcomes.

- 1. Palmer et al. Meta-analysis: Erythropoiesis-Stimulating Agents in Patients with Chronic Kidney Disease. *Ann Intern Med.* 2010;153:23-33.
- 2. Phrommintikul A et al. "Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis." *The lancet* 369.9559 (2007): 381-388.
- 3. Koulouridis, Ioannis, et al. "Dose of erythropoiesis-stimulating agents and adverse outcomes in CKD: a metaregression analysis." *American Journal of Kidney Diseases* 61.1 (2013): 44-56.

Identification of all appropriate trials was confirmed through a literature search (www.pubmed.gov) using combinations of the terms "ESA", "epoetin", "CKD", "ESRD", "placebo", and "anemia".

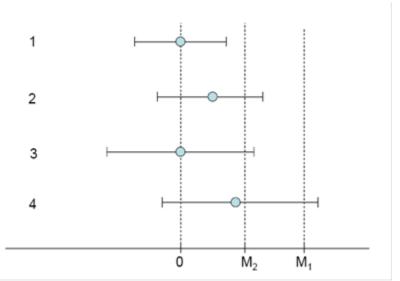
The approach taken for this NI margin is the fixed margin method described in the U.S. Food and Drug Administration's 2010 guidance "Non-Inferiority Clinical Trials." In this guidance, the fixed margin approach is summarized thus:

"Briefly, in the fixed margin method, the margin M_1 is based upon estimates of the effect of the active comparator in previously conducted studies, making any needed adjustments

for changes in trial circumstances. The NI margin is then pre-specified and it is usually chosen as a margin smaller than M_1 (i.e., M_2), because it is usually felt that for an important endpoint a reasonable fraction of the effect of the control should be preserved. The NI study is successful if the results of the NI study rule out inferiority of the test drug to the control by the NI margin or more. It is referred to as a fixed margin analysis because the past studies comparing the drug with placebo are used to derive a single fixed value for M_1 , even though this value is based on results of placebo-controlled trials (one or multiple trials versus placebo) that have a point estimate and confidence interval for the comparison with placebo. The value typically chosen is the lower bound of the 95% CI (although this is potentially flexible) of a placebo-controlled trial or meta-analysis of trials. This value becomes the margin M_1 , after any adjustments needed for concerns about constancy.

The fixed margin M_1 , or M_2 if that is chosen as the NI margin, is then used as the value to be excluded for C-T in the NI study by ensuring that the upper bound of the 95% CI for C-T is $< M_1$ (or M_2). This 95% lower bound is, in one sense, a conservative estimate of the effect size shown in the historical experience. It is recognized, however, that although we use it as a "fixed" value, it is in fact a random variable, which cannot invariably be assumed to represent the active control effect in the NI study." This approach is shown schematically in Figure 2.

Figure 2 Active Control – Test Drug differences (Point estimate, 95% CI)



- "1. C-T point estimate = 0 and upper bound of 95% CI < M2, indicating test drug is effective (NI demonstrated).
- 2. Point estimate of C-T favors C and upper bound of 95% CI < M1 but > M2, indicating effect > 0 but unacceptable loss of the control effect.
- 3. Point estimate of C-T is zero and upper bound of 95% CI < M1 but it is slightly greater than M2. Judgment could lead to conclusion of effectiveness.

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4. C-T point estimate favors C and upper bound of 95% CI > M1, indicating there is no evidence of effectiveness for test drug."

Table 13 below displays the mean change in hemoglobin for recombinant human (EPO) based on 3 publications, [Canadian et al, 1990], [Bennett et al, 1991] and [Nissenson et al, 1995]. The 3 studies are all randomized, double-blinded, randomized, placebo controlled study to evaluate the effect EOP (epoetin alfa or beta) in anemia patient with renal End Stage Renal Disease with Peritoneal Dialysis or Hemodialysis.

Using the data in Table 13 below, the weighted mean of the point estimate of treatment effect in mean change from baseline for EPO (mean change in hemoglobin or hemoglobin equivalence in EPO group — mean change in placebo group) was calculated, along with its 95% confidence interval.

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Table 13 Historical studies with mean change and SD in hematocrit or hemoglobin available in End Stage Renal Disease (ESRD): EPO versus Placebo

Nissenson et al, 1995 (Erythropoietin in Peritoneal	Endpoint	EPO Mean (SD)	Placebo Mean (SD)	EPO-Placebo Mean (Std Err)
Dialysis)		sample size =	Sample size =	
		78	74	
	Baseline in hematocrit	23.8 (3.8) %	23.8 (3.3) %	
	12 week Follow up in hematocrit	33.7 (4.8) %	24.1 (3.8)	
	HMG equivalent Mean Change*	3.3(0.33) g/dL	0.1(0.17) g/dL	3.2(0.042) g/dL
Bennett et al, 1991 (Epoetin Beta - Hemodialysis)		sample size = 90	sample size = 41	
	Baseline	7.1 (0.1*sqrt(90)) g/dL	6.8 (0.2*sqrt(41)) g/dL	
	12 week Follow up	11.1 (0.2*sqrt(90)) g/dL	7.6 (0.3*sqrt(41)) g/dL	
	HMG Mean Change*	4.0 (0.95) g/dL	0.8(0.64) g/dL	3.2(0.141) g/dL
Canadian et al, 1990 (Erythropoietin - hemodialysis patients)		sample size = 40	sample size = 40	
	Baseline	7.1 (0.9) g/dL	6.9 (1.0) g/dL	
	6 month follow up	10.2 (1.0) g/dL	7.4(1.2) g/dL	
	HMG Mean Change*	3.1(0.1) g/dL	0.5 (0.2) g/dL	2.6(0.035) g/dL

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*Hematocrit in % was converted to Hemoglobin in g/dL by dividing by 3. Due to the information are limited from the reference, the mean change in hemoglobin and the corresponding standard deviation were derived where the baseline and follow up hemoglobin were assumed to be independent which is very conservative.

The weighted mean point estimate for mean change from baseline in hemoglobin for EPO (mean change from baseline in hemoglobin for EPO group – mean change from baseline in hemoglobin for placebo group) was estimated to be 2.859 g/dL by treating the studies as fixed effect, with a 95% confidence interval of (2.806, 2.911) and 2.993 g/dL by treating the studies as random effect, with a 95% confidence interval of (2.520, 3.466) from meta-data analysis. The lower bound of this 95% confidence interval by treating the study as random effect, 2.520 is taken to be the NI margin M₁. To ensure that not more than 50% of the effect of EPO was lost, giving an NI margin (M₂) of 1.26. However, a very conservative M₂ margin was chosen, 0.75, which is 29.76% of M₁, thus ensuring preservation of 70.24% of M₁ in this study.

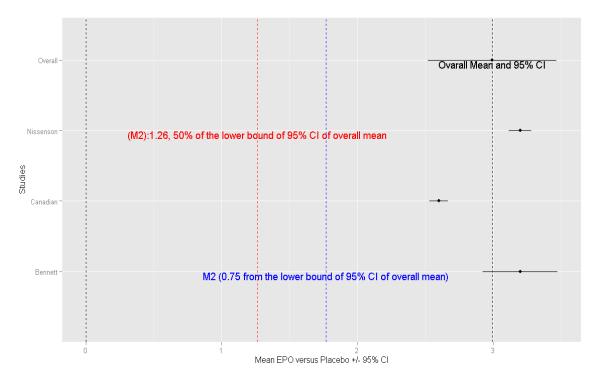
While for study with responder as the primary endpoint, Roth et al 1994 study results were used to calculate the NI margin. The study was undertaken to ascertain the effects of recombinant human erythropoietin (EPO) on renal function in chronic renal failure predialysis patients. The study defined an increase to a hematocrit of at least 36% (Hemoglobin > 12 g/dL) as correction or responder. There are total 43 subjects in EPO treatment group and 40 in the placebo group. Out of 43 subjects in EPO treatment group, 34 subjects were responder and none were responders from placebo group.

95% CI (66.9, 91.2) % was calculated for the estimated difference in responder rate, 79.1%. The lower bound of this 95% confidence interval 0.669 is taken to be the NI margin M₁. To ensure that not more than 50% of the effect of EPO was lost, giving an NI margin (M₂) of 0.335. Similarly, a very conservative M₂ margin was chosen, 0.15, which is 22.42% of M₁, thus ensuring preservation of 77.58% of M₁ in this study.

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Figure 2 Active Control – Placebo differences (Point estimate, 95% CI) in History Studies



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16.7 APPENDIX 7: TEMPEROAL PROFILE OF TEAES OF SPECIAL INTEREST

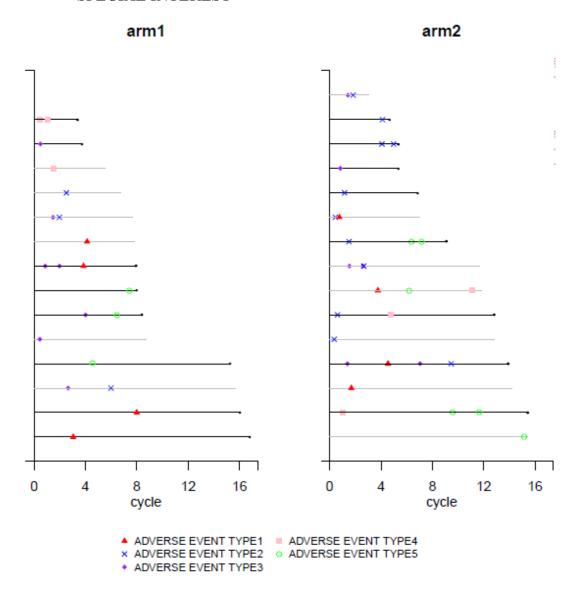


EXHIBIT E



Investors and Media

Press Release



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FibroGen Announces Positive Topline Results from Three Global Phase 3 Trials of Roxadustat for Treatment of Anemia in Patients with Chronic **Kidney Disease**

Primary efficacy endpoints met in all three studies: non-dialysis, incident dialysis, and stable dialysis studies

SAN FRANCISCO, Dec. 20, 2018 (GLOBE NEWSWIRE) -- FibroGen, Inc. (NASDAQ:FGEN), a leading biopharmaceutical company discovering and developing a pipeline of first-in-class therapeutics, today announced that roxadustat, an inhibitor of hypoxia-inducible-factor (HIF) prolyl hydroxylase activity (HIF-PHI), met all primary efficacy endpoints in the three global pivotal Phase 3 trials conducted by FibroGen: ANDES in non-dialysis-dependent (NDD) chronic kidney disease (CKD) patients, HIMALAYAS in incident (newly initiated) dialysis patients, and SIERRAS in dialysis-dependent (DD) CKD patients.

"Anemia in CKD is a serious condition for which a significant number of patients are left without treatment options in many markets," said Thomas B. Neff, Chief Executive Officer, FibroGen. "These Phase 3 results demonstrate the potential for roxadustat to be a first-in-class oral anemia therapeutic for CKD patients. This is the first well-controlled CKD anemia program that has shown improved efficacy in incident and stable dialysis patients relative to ESA standard of care therapy."

Each of the three studies had a pre-specified primary efficacy endpoint for meeting U.S. regulatory requirements and another pre-specified primary efficacy endpoint for meeting EU regulatory requirements, which also served as a secondary efficacy endpoint for the U.S. Both the U.S. and EU primary efficacy endpoints were met in all three studies.

Non-Dialysis CKD Patients Study (ANDES¹)

ANDES is a 922-patient global Phase 3, randomized, double-blinded, placebo-controlled trial designed to evaluate the efficacy and safety of roxadustat versus placebo for the treatment of anemia in patients with later-stage CKD (stages 3, 4 or 5) who are not dialysis-dependent. This study was conducted in the U.S. and 14 other countries. Treatment duration was up to 4.5 years, with average duration of 1.7 years. Baseline hemoglobin (Hb) levels averaged 9.1 g/dL in both the roxadustat (N=616) and the placebo (N=306) arms.

- a. U.S. primary efficacy endpoint: Roxadustat was superior to placebo in mean Hb change from baseline to the average over Weeks 28-52 (2.00 vs 0.16 g/dL, respectively, p<0.0001).
- b. EU primary efficacy endpoint: A higher proportion of roxadustat-treated patients (86.0%) achieved a Hb response in the first 24 weeks (defined as achieving a Hb level of at least 11 g/dL and a Hb increase of at least 1 g/dL) as compared to placebo (6.6%), p=0.0007.

Furthermore, in a pre-specified secondary efficacy analysis, roxadustat reduced the risk of rescue therapy by 81% (hazard ratio (HR)=0.19) defined as the time to first use of blood transfusion, administration of an erythropoiesis stimulating agent (ESA) or IV iron in the first 52 weeks of treatment, p<0.0001. In addition, roxadustat reduced the risk of blood transfusion by 74% (HR = 0.26) in the time to first blood transfusion during the first 52 weeks of treatment, p<0.0001.

Incident Dialysis CKD Patients Study (HIMALAYAS²)

HIMALAYAS is a 1,043-patient global Phase 3 randomized, open-label, active-controlled trial to assess the efficacy and safety of roxadustat compared to epoetin alfa, an ESA, for the treatment of anemia in CKD patients who have newly initiated dialysis treatment for end stage renal disease and have had minimal or no exposure to ESA prior to study participation.² This study was conducted in the U.S. and 17 other countries. Treatment duration was up to 4.4 years, with mean duration of 1.8 years. Mean baseline Hb was 8.43 g/dL in the roxadustat arm (N=522) and 8.46 g/dL in the epoetin alfa arm (N=521).

- a. U.S. primary efficacy endpoint: The mean Hb change from baseline to the average over Weeks 28-52 was 2.57 g/dL (roxadustat) vs. 2.36 g/dL (epoetin alfa), a least squares mean difference of 0.18 g/dL, with the 95% confidence interval (CI) of (0.08, 0.29). The non-inferiority criteria was met as the lower bound of the 95% CI was well above the non-inferiority margin of -0.75 g/dL, and superiority over epoetin alfa was also achieved, p=0.0005.
- b. EU primary efficacy endpoint: Roxadustat met the non-inferiority criteria compared to epoetin alfa: 88.2% of the roxadustat-treated patients achieved a Hb response in the first 24 weeks (defined as achieving a Hb level of at least 11 g/dL and a Hb increase of at least 1 g/dL) compared to an 84.5% responder rate in the epoetin alfa arm; lower bound of the 95% CI (-0.9%, 7.6%) of the treatment difference in responder rate is well above the non-inferiority margin of -15%.

Stable Dialysis CKD Patients Study (SIERRAS³)

SIERRAS is a 741-patient U.S. Phase 3, randomized, open-label, active-controlled trial to assess the efficacy and safety of roxadustat compared to epoetin alfa for the treatment of anemia (in maintaining Hb level) in DD-CKD patients who were receiving stable doses of ESA prior to study participation.³ Treatment duration was up to 3.5 years, with a mean duration of 1.9 years. Mean baseline Hb levels were 10.3 g/dL in both roxadustat and epoetin alfa arms.

- a. U.S. primary efficacy endpoint: The mean Hb change from baseline to the average over Weeks 28-52 was 0.39 g/dL (roxadustat) vs -0.09 g/dL (epoetin alfa), a least squares mean treatment difference of 0.48 g/dL (95% CI 0.37, 0.59). Roxadustat met the non-inferiority criteria as the lower bound of 95% CI was well above the non-inferiority margin of -0.75 g/dL. Roxadustat also achieved superiority, p<0.0001.
- b. EU primary efficacy endpoint: The mean Hb change from baseline to the average over Weeks 28-36 was 0.54 g/dL (roxadustat) vs -0.02 g/dL (epoetin alfa), a least squares mean treatment difference of 0.53 g/dL with a 95% CI (0.39, 0.67). Roxadustat met the non-inferiority criteria as the lower bound of the 95% CI was well above the non-inferiority margin of -0.75 g/dL. Roxadustat also achieved superiority over epoetin alfa, p<0.0001.

In addition, in the pre-specified secondary efficacy analysis, roxadustat-treated patients had a 33% reduction in the risk of blood transfusion compared to epoetin alfa (HR=0.67) in the time to first blood transfusion during treatment, p=0.0337.

The preliminary safety analyses of each of these three individual studies show an overall safety profile consistent with the results observed in prior roxadustat studies. The adverse events reported are consistent with those expected in these study populations with similar background diseases.

These three Phase 3 studies sponsored and conducted by FibroGen are part of FibroGen's codevelopment collaboration with AstraZeneca AB and with Astellas Pharma Inc. These studies are part of the roxadustat global Phases 3 program, which consists of multiple global studies in more Results of the pooled safety analyses, including the major adverse cardiovascular events (MACE) for both NDD-CKD and DD-CKD in the global Phase 3 program is anticipated prior to U.S. NDA submission in the first half of 2019.

"We are excited to have achieved superiority in efficacy not only against placebo but also over active comparator in our studies," said K. Peony Yu, MD, Chief Medical Officer, FibroGen. "These results support roxadustat's potential to bring clinical benefit over current standard of care, such as reducing blood transfusion risk in patients on dialysis and those not on dialysis, and to improve patient access to anemia therapy with a new convenient oral therapeutic."

AstraZeneca also announced positive topline results today from its roxadustat phase 3 trials; OLYMPUS⁴ in NDD-CKD and ROCKIES⁵ in DD-CKD.

About Anemia Associated with CKD

Anemia can be a serious medical condition in which patients have insufficient red blood cells and low levels of Hb, a protein in red blood cells that carries oxygen to cells throughout the body. Anemia in CKD is associated with increased risk of hospitalization, cardiovascular complications and death, also frequently causing significant fatigue, cognitive dysfunction and reduced quality of life. Severe anemia is common in patients with CKD, cancer, myelodysplastic syndromes (MDS), inflammatory diseases, and other serious illnesses.

Anemia is particularly prevalent in patients with CKD. The prevalence of CKD in the adult population is estimated at 10-12% globally, ¹⁰ and is generally a progressive disease characterized by gradual loss of kidney function that may eventually lead to kidney failure, or end stage renal disease, requiring dialysis or kidney transplant to survive. Blood transfusion is used for treating life-threatening severe anemia. However, blood transfusions reduce the patient's opportunity for kidney transplant, increase risk of infections and the risk of complications such as heart failure and allergic reactions.

According to the United States Renal Data System (USRDS), over 14% of the U.S. adult population is affected by CKD, and a majority of dialysis-eligible CKD patients are currently on dialysis. It is estimated that approximately 507,000 patients are receiving dialysis in the U.S. as of 2016.¹¹

About Roxadustat

Roxadustat (FG-4592), discovered by FibroGen, is a first-in-class, orally administered small molecule currently approved in China for the treatment of anemia in CKD patients on dialysis. Roxadustat is a HIF-PHI that promotes erythropoiesis through increasing endogenous production of erythropoietin, improving iron regulation, and overcoming the negative impact of inflammation on hemoglobin syntheses and red blood cell production by downregulating hepcidin. Administration of roxadustat has been shown to induce coordinated erythropoiesis, increasing red blood cell count while maintaining plasma erythropoietin levels within or near normal physiologic range in multiple subpopulations of CKD patients, including in the presence of inflammation and without a need for supplemental intravenous iron.

FibroGen and collaboration partners are pursuing four approval pathways in major jurisdictions to prepare for commercialization worldwide:

- Astellas and FibroGen are collaborating on the development and commercialization of roxadustat for the treatment of anemia in territories including Japan, Europe, the Commonwealth of Independent States, the Middle East, and South Africa.
- AstraZeneca and FibroGen are collaborating on the development and commercialization of roxadustat for the treatment of anemia in the U.S., China, and other markets in the Americas and in Australia/New Zealand as well as Southeast Asia.

FibroGen and its partners have completed 35 Phase 1 and Phase 2 studies. The Phase 2 clinical studies have consistently demonstrated anemia correction and maintenance of hemoglobin levels in multiple subpopulations across a wide spectrum of CKD patients.

Globally, the Phase 3 program encompasses a total of 15 Phase 3 studies of roxadustat in both non-dialysis-dependent and dialysis-dependent CKD patients to support independent regulatory approvals in the U.S., Europe, Japan, and China. To date, positive topline results have been announced for 12 of the Phase 3 studies, with two supporting the China NDA for treatment of anemia in CKD patients on dialysis and not on dialysis, four supporting the Japan NDA for treatment of anemia in CKD patients on dialysis, and six supporting the U.S./EU submissions including today's announcement of 3 studies by FibroGen. Roxadustat was approved by China National Medical Products Administration (NMPA) in December 2018, for treatment of anemia in CKD patients on dialysis. The Japan NDA submitted by Astellas is under review by the Japan Pharmaceuticals and Medical Devices Agency (PMDA).

Roxadustat is currently in Phase 3 clinical development for the treatment of anemia associated with MDS in the U.S. and in Phase 2/3 development for MDS in China.

About FibroGen

FibroGen, Inc., headquartered in San Francisco, California, with subsidiary offices in Beijing and Shanghai, People's Republic of China, is a leading biopharmaceutical company discovering and developing a pipeline of first-in-class therapeutics. The company applies its pioneering expertise in hypoxia-inducible factor (HIF), connective tissue growth factor (CTGF) biology, and clinical development to advance innovative medicines for the treatment of anemia, fibrotic disease, and cancer. Roxadustat, the company's most advanced product candidate, is an oral small molecule inhibitor of HIF prolyl hydroxylase activity, completing worldwide Phase 3 clinical development for the treatment of anemia in chronic kidney disease (CKD), with a New Drug Application (NDA) now approved by the National Medical Products Administration (NMPA) in China. Our partner Astellas submitted a NDA for the treatment of anemia in CKD patients on dialysis in Japan in September 2018, which is currently under review by the Pharmaceuticals and Medical Devices Agency (PMDA). Roxadustat is in Phase 3 clinical development in the U.S. and Europe and in Phase 2/3 development in China for anemia associated with myelodysplastic syndromes (MDS). Pamrevlumab, an anti-CTGF human monoclonal antibody, is advancing towards Phase 3 clinical development for the

treatment of idiopathic pulmonary fibrosis (IPF) and pancreatic cancer, and is currently in a Phase 2 trial for Duchenne muscular dystrophy (DMD). FibroGen is also developing a biosynthetic cornea in China. For more information, please visit www.fibrogen.com.

Forward-Looking Statements

This release contains forward-looking statements regarding our strategy, future plans and prospects, including statements regarding the development of the company's product candidates pamrevlumab and roxadustat, the potential safety and efficacy profile of our product candidates, and our clinical, regulatory plans, and those of our partners. These forward-looking statements include, but are not limited to, statements about our plans, objectives, representations and contentions and are not historical facts and typically are identified by use of terms such as "may," "will", "should," "on track," "could," "expect," "plan," "anticipate," "believe," "estimate," "predict," "potential," "continue" and similar words, although some forward-looking statements are expressed differently. Our actual results may differ materially from those indicated in these forward-looking statements due to risks and uncertainties related to the continued progress and timing of our various programs, including the enrollment and results from ongoing and potential future clinical trials, and other matters that are described in our Annual Report on Form 10-K for the fiscal year ended December 31, 2017, and our Quarterly Report on Form 10-Q for the fiscal quarter ended September 30, 2018 filed with the Securities and Exchange Commission (SEC), including the risk factors set forth therein. Investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date of this release, and we undertake no obligation to update any forward-looking statement in this press release, except as required by law.

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FibroGen, Inc

EXHIBIT F

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Phase III OLYMPUS and ROCKIES trials for roxadustat met their primary endpoints in chronic kidney disease patients with anaemia

PUBLISHED 20 December 2018

20 December 2018 07:00 GMT

This announcement contains inside information

OLYMPUS demonstrated a statistically-significant and clinically-meaningful improvement in haemoglobin vs. placebo in non-dialysis-dependent patients

ROCKIES demonstrated a statistically-significant improvement in haemoglobin vs. epoetin alfa in dialysis-dependent patients

AstraZeneca today announced that the Phase III OLYMPUS and ROCKIES trials for roxadustat each met their primary efficacy endpoints for the treatment of patients with anaemia in chronic kidney disease (CKD) that are either non-dialysis-dependent or dialysis-dependent, respectively. Roxadustat is a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) and a potential firstin-class new medicine to treat anaemia in CKD being jointly developed and commercialised by AstraZeneca and FibroGen, Inc.

OLYMPUS is a Phase III, randomised, double-blinded, placebo-controlled trial designed to evaluate the efficacy and safety of roxadustat vs. placebo for the treatment of patients with anaemia in CKD stages 3, 4 and 5 whose disease progression is moderate to severe and who are non-dialysis dependent. The trial met its primary efficacy endpoint by demonstrating a statisticallysignificant and clinically-meaningful improvement in mean change from baseline in haemoglobin (Hb) levels averaged over weeks 28 to 52 vs. placebo. The trial evaluated 2,781 patients in 26 countries.

ROCKIES is a Phase III, randomised, open-label, active-controlled trial designed to assess the efficacy and safety of roxadustat vs. epoetin alfa, for the treatment of patients with anaemia in CKD who are dialysis dependent. The trial met its primary efficacy endpoint by demonstrating a statistically-significant improvement in mean change from baseline in Hb levels averaged over weeks 28 to 52 vs. epoetin alfa.² The trial evaluated 2,133 patients in 18 countries.

The global Phase III programme consists of more than 9,000 patients in trials conducted by AstraZeneca, FibroGen and Astellas. In September 2018, Astellas announced high-level results from the Phase III ALPS trial. FibroGen and Astellas anticipate reporting high-level results from their remaining trials in due course. These trials will contribute to the combined pooled safety analysis, including major adverse cardiovascular event (MACE) outcomes, anticipated during H1 2019.

Sean Bohen, Executive Vice-President, Global Medicines Development and Chief Medical Officer, said: "These results add to the growing body of evidence for roxadustat, which is part of the largest clinical programme worldwide in evaluating the novel class of HIF-PHI. This is a significant milestone in the role roxadustat can play to help address a high unmet need in anaemia associated with chronic kidney disease, which today is under diagnosed and in many cases under treated."

Data from the Phase III OLYMPUS and ROCKIES trials, together with the efficacy and pooled safety data from the global Phase III programme, will be part of the regulatory submission package in the US and other major countries. Results from these trials will be presented at forthcoming medical meetings.

About roxadustat

Roxadustat is a first-in-class, orally-administered small-molecule medicine recently approved in China for the treatment of patients with anaemia from CKD on dialysis. Roxadustat is a HIF-PHI that promotes erythropoiesis by increasing endogenous production of erythropoietin and improving iron regulation and overcoming the negative impact of inflammation on haemoglobin synthesis and red blood cell production by downregulating hepcidin. Administration of roxadustat has been shown to induce coordinated erythropoiesis, increasing red blood cell count while maintaining plasma erythropoietin levels within or near normal physiologic range, in multiple subpopulations of

CKD patients, including in the presence of inflammation and without a need for supplemental intravenous (IV) iron.

AstraZeneca and FibroGen, Inc. are collaborating on the development and commercialisation of roxadustat for the treatment of anaemia in patients with CKD in the US, China, and other global markets. FibroGen and Astellas are collaborating on the development and commercialisation of roxadustat for the treatment of anaemia in patients with CKD in Japan, Europe, the Commonwealth of Independent States, the Middle East, and South Africa.

About anaemia in CKD

Anaemia can be a serious medical condition in which patients have insufficient red blood cells and low levels of Hb, a protein in red blood cells that carries oxygen to cells throughout the body.^{3,4} Anaemia in CKD is associated with increased risk of hospitalisation, cardiovascular complications and death.⁵ also frequently causing significant fatigue, cognitive dysfunction and decreased quality of life. 6 Severe anaemia is common in patients with CKD, cancer, myelodysplastic syndrome, inflammatory diseases, and other serious illnesses.

Anaemia is particularly prevalent in patients with CKD, which affects more than 200 million people worldwide and is generally a progressive disease characterised by gradual loss of kidney function that may eventually lead to kidney failure.

In the US, according to the United States Renal Data System (USRDS), a majority of dialysiseligible CKD patients are currently on dialysis. Of the approximately 507,000 patients receiving dialysis in the US as of 2016, approximately 80% were being treated with ESAs for anaemia. Patients seldom receive ESA treatment until they initiate dialysis therapy.

About FibroGen

FibroGen, Inc., headquartered in San Francisco, California, with subsidiary offices in Beijing and Shanghai, People's Republic of China, is a leading biopharmaceutical company discovering and developing a pipeline of first-in-class therapeutics. The company applies its pioneering expertise in hypoxia-inducible factor (HIF), connective tissue growth factor (CTGF) biology, and clinical development to advance innovative medicines for the treatment of anemia, fibrotic disease, and cancer. Roxadustat, the company's most advanced product candidate, is an oral small molecule inhibitor of HIF prolyl hydroxylase activity, completing worldwide Phase 3 clinical development for the treatment of anemia in chronic kidney disease (CKD), with a New Drug Application (NDA) now approved by the National Medical Products Administration (NMPA) in China. FibroGen's partner Astellas submitted an NDA for the treatment of anemia in CKD patients on dialysis in Japan in September 2018, currently under review by the Pharmaceuticals and Medical Devices Agency (PMDA). Roxadustat is in Phase 3 clinical development in the U.S. and Europe and in Phase 2/3 development in China for anemia associated with myelodysplastic syndromes (MDS). Pamrevlumab, an anti-CTGF human monoclonal antibody, is advancing towards Phase 3 clinical development for the treatment of idiopathic pulmonary fibrosis (IPF) and pancreatic cancer, and is currently in a Phase 2 trial for Duchenne muscular dystrophy (DMD). FibroGen is also developing a biosynthetic cornea in China. For more information, please visit <u>www.fibrogen.com</u>.

About AstraZeneca in Cardiovascular, Renal & Metabolism (CVRM)

Cardiovascular, renal and metabolism together form one of AstraZeneca's main therapy areas and a key growth driver for the Company. By following the science to understand more clearly the underlying links between the heart, kidneys and pancreas, AstraZeneca is investing in a portfolio of medicines to protect organs and improve outcomes by slowing disease progression, reducing risks and tackling co-morbidities. Our ambition is to modify or halt the natural course of CVRM diseases and potentially regenerate organs and restore function, by continuing to deliver transformative

science that improves treatment practices and cardiovascular health for millions of patients worldwide.

About AstraZeneca

AstraZeneca is a global, science-led biopharmaceutical company that focuses on the discovery, development and commercialisation of prescription medicines, primarily for the treatment of diseases in three therapy areas - Oncology, Cardiovascular, Renal & Metabolism and Respiratory. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. For more information, please visit astrazeneca.com and follow us on Twitter @AstraZeneca.

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S&P Global Market Intelligence

FibroGen, Inc. NasdaqGS:FGEN FQ4 2018 Earnings Call Transcripts

Wednesday, February 27, 2019 10:00 PM GMT

S&P Global Market Intelligence Estimates

	-FQ4 2018-		-FQ1 2019-	-FY 2018-			-FY 2019-	
	CONSENSUS	ACTUAL	SURPRISE	CONSENSUS	CONSENSUS	ACTUAL	SURPRISE	CONSENSUS
EPS Normalized	0.09	0.23	155.56	(0.58)	(1.37)	(1.03)	NM	(1.78)
Revenue (mm)	72.15	108.05	4 9.76	37.94	177.01	212.96	▲20.31	233.39

Currency: USD

Consensus as of Feb-11-2019 5:17 AM GMT

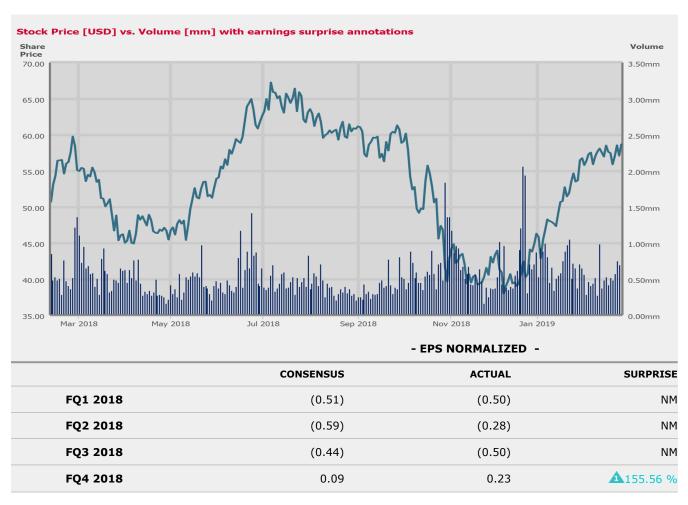


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Presentation

Operator

Welcome to the FibroGen's Fourth Quarter and Full Year 2018 Financial Results Conference Call. My name is Adrienne, and I'll be your operator for today's call. [Operator Instructions] Please note this conference is being recorded. For opening remarks and introduction, I'll now turn the call over to Karen Bergman, Vice President, Investor Relations and Corporate Communications.

Karen L. Bergman

Vice President of Investor Relations & Corporate Communications

Adrienne, thank you, and good afternoon, everyone. Thank you so much for joining our call today. We are reporting financial results and corporate update for the fourth quarter and full year 2018. Joining me today on the call are Tom Neff, Chairman and Chief Executive Officer; Dr. Peony Yu, Chief Medical Officer; Ms. Chris Chung, Senior Vice President, China Operations; Dr. Elias Kouchakji, Senior Vice President, Clinical Development, Drug Safety and Pharmacovigilance; and Mr. Pat Cotroneo, Chief Financial Officer. Following our prepared remarks, Tom will discuss upcoming milestones and we will open the call to Q&A.

During this call, we may make forward-looking statements regarding our business, including our collaborations with AstraZeneca and Astellas; financial guidance; the initiation, enrollment, design, conduct and results of clinical trials; our regulatory strategies and potential regulatory results; our research and development activities; and certain other business matters. For risks and uncertainties regarding our business and statements made on the call today as well as factors beyond our control that may cause differences between current expectations and actual results, we refer you to our annual report on Form 10-K for the fiscal year ended December 31, 2018, filed with the Securities and Exchange Commission. Copies of these filings can be found in the Investors section of our website. We undertake no obligation to update any forward-looking statement whether as a result of new information, future developments or otherwise.

The format for today's call includes remarks from FibroGen's management team, and then we'll open the lines to take your questions. The press release reporting our financial results and business update and a webcast of today's conference call can be found on the Investors section of FibroGen's website at www.fibrogen.com. The webcast will be available for 2 weeks from today's date.

And with that, I'd now like to turn the call over to our CEO, Tom Neff.

Thomas B. Neff

Founder, Chairman & CEO

Welcome, everyone, and thank you for joining us. In the period since our last quarterly call, we have been very, very busy. Let me begin with an update of key accomplishments over the last 90 days.

On December 17, 2018, we received our first regulatory approval for roxadustat from the National Medical Products Administration of the People's Republic of China for anemia and dialysis stage patients with chronic kidney disease, or CKD, including patients on hemodialysis and peritoneal dialysis. Not only is China the first country to approve roxadustat, but this represents a number of other incredible first for FibroGen for innovation in China and for the CKD patients with anemia. We are commencing a variety of commercial activities in China in the next few months and plan to launch in the third quarter of 2019.

Following very shortly after the China approval news, on December 19 -- 20, we and our partner, AstraZeneca, announced top line results from our global Phase III program for roxadustat in dialysis patients, previously using EPO, Study 064 or SIERRAS; as well as newly initiated dialysis or incident dialysis in Study 063 or HIMALAYAS; and finally the non-dialysis-dependent stage CKD patients in the ANDES study. In these 5 U.S. ROW studies, we enrolled a total of 7,721 patients composed of 3,917 in dialysis and 3,804 in non-dialysis. All of these studies have positive top line results. We and our partners believe the results from these trials to support our NDA in U.S. Food and Drug Administration as well

as our marketing authorization application, or MAA, to the European Medicines Authority, or EMA. The fully adjudicated MACE results, including completing adjudication procedures to enable consistent safety assessment without bias, are to be included in our planned NDA to the FDA. Completion of the full adjudication procedures is on track for the second quarter of 2019.

In non-dialysis, we include the Astellas' Study 608. We have a total of a little bit over 4,300 patients in the study population, which may be the largest CKD population not on dialysis to have been studied in a prospective clinical program where outcomes are measured against placebo. There is a rich and diverse set of extremely interesting preliminary data emerging, including data regarding renal progression as well as quality of life, each of which Peony will describe in more detail later. At this point, based on our review of the data to date and our discussions with counterpart teams at AZ and Astellas and discussions with our partners' leadership, there is a strong conviction to move ahead to file the NDA and MAA this year.

Apart from the first approval in China and reporting the top line data in the 5 Phase III studies, I am also very pleased to report that in Japan, Astellas submitted an NDA for the treatment of anemia in CKD patients on dialysis in September 2018, which is currently under review by PMDA, or the Pharmaceutical and Medical Devices Agency, in Japan. The PMDA decision on this NDA submission is expected in second half 2019.

Now let me turn to myelodysplastic syndromes or MDS. Beyond anemia and CKD, roxadustat is systematically being evaluated in other indications, the first of which is MDS. In our ongoing U.S./EU Phase III study, where we're looking at elimination of transfusion requirement for a period of 8 months or -- I'm sorry, 8 weeks or longer as the end point and then in China the Phase II/III study end points to demonstrate effectiveness with respect to hemoglobin by increasing it by 1.5 grams a deciliter or more. In the open label portion of the U.S./EU study, we are seeing very good data, as reflected in decisions we and our partners have made to move forward with the double-blind, placebo-controlled portion of this Phase III study. In China, we have seen several treatment successes and enrollment in the open label portion, where we are recruiting up to 40 patients. It's ongoing. We are moving ahead in our Phase II program in chemotherapy-induced anemia, or CIA, in the U.S. and both of our partners are supportive in this regard.

Turning to pamrevlumab. We are excited to report the start of Phase III studies in 2 indications where patients truly have limited or no treatment options available: locally advanced unresectable pancreatic cancer, or LAPC; and idiopathic pulmonary fibrosis, or IPF. Elias will speak to these studies more later on, on this call. During 2018, in LAPC, we presented promising clinical results from the Phase II study at the 2018 ASCO meeting that supported our Phase III study design to test pamrevlumab in combination with chemotherapy as a neoadjuvant treatment for unresectable patients. In IPF, positive efficacy and safety results from our Phase IIb study were reported at ATS, ERS and ICLAF conferences in 2018. The U.S. FDA granted Fast Track designation to pamrevlumab in 2018 for both locally advanced unresectable pancreatic cancer and idiopathic pulmonary fibrosis.

Turning to our pamrevlumab program in Duchenne muscular dystrophy, or DMD. We are evaluating nonambulatory patients. This means boys of the age of 12 or 13 being put into wheelchairs and time period thereafter during adolescence. We completed enrollment in 2018 of our Phase II study and will complete the first full year of treatment this March for all patients enrolled. I would like to emphasize that there is no specific approved product for non-ambulatory DMD population, which consists primarily of young boys who will, in all eventuality, progress to this stage by age 12, 13. We expect to see some very interesting data from the first year of treatment starting in April.

Let me finish here by addressing some top-level finance results. Pat Cotroneo, our CFO, will provide more detail later on in the call. In the fourth guarter of 2018, we reported \$21 million of net income or \$0.23 per fully diluted share in EPS terms. As of December 31, 2018, FibroGen had \$747.2 million in cash. And again, here, Pat will provide more detail later on the call.

I would now like to turn this over to Dr. Peony Yu for updates on the anemia program. Peony, please.

K. Peony Yu

Chief Medical Officer

Thank you, Tom. The China health authority's approval of roxadustat for the treatment of anemia in dialysis-dependent CKD patients, the first approval of any HIF-PHI in the world is a great start for bringing our novel anemia treatment to patients, which was discovered and developed here at FibroGen.

For the roxadustat program in the U.S. and Europe, we and our partners, AstraZeneca and Astellas, have announced completion of all studies needed for NDA and for MAA. FibroGen and AstraZeneca have announced positive top line results in our CKD Phase III studies just before year-end, and Astellas has also announced primary efficacy end points were met in all of their Phase III studies. I shall highlight some key exciting findings on this call.

First of all, these Phase III studies demonstrated roxadustat's efficacy. We met the primary efficacy end point in each of the 3 CKD non-dialysis studies, ANDES by FibroGen, OLYMPUS by AstraZeneca and ALPS by Astellas, by demonstrating superiority of roxadustat compared to placebo in the change in hemoglobin level from baseline, the hemoglobin averaged over weeks 28 to 52. In the Phase III dialysis studies, non-inferiority criteria were met in primary end point comparing hemoglobin change in roxadustat-treated patients with those on EPO alfa, which is the current standard of care in dialysis and in CKD patients. And furthermore, superiority was demonstrated in all 3 dialysis studies. These are HIMALAYAS and SIERRAS by FibroGen, and ROCKIES by AstraZeneca.

Also, much clinical importance, roxadustat-treated patients had significant reduction in red blood cell transfusion risk, which was measured by time to first transfusion when compared to placebo in CKD non-dialysis studies -- non-dialysis patient in the ANDES studies. Moreover, in active control trial in SIERRAS study, our U.S. dialysis conversion study in which patients were randomized to receive roxadustat or to continue stable maintenance dose of epoetin alfa, roxadustat was also shown to have a lower transfusion risk than ESA.

Other than the usual risks, such as infections or iron overload resulting from transfusion, red blood cell transfusion is known to reduce CKD patients' eligibility for a kidney transplant because of higher risk of rejection caused by associated alloimmunization. Kidney transplant is the preferred option for patients with end-stage kidney disease because of longer survival than chronic dialysis. This is why transfusion reduction is such a big deal and -- could be of great clinical significance to CKD patients.

We previously reported results from our China Phase III dialysis study that show roxadustat was effective in the presence of inflammation, as measured by CRP, with no increase in dose requirements, whereas the current EPO had lower effectiveness in inflamed patients despite higher doses. What we find in these large U.S. Phase III studies is consistent with this differentiation from ESA in the presence of inflammation. In both our HIMALAYAS and SIERRAS studies, roxadustat was shown to be effective regardless of the patient's inflammatory status as the mean achieved hemoglobin level and roxadustat dose requirements were comparable between patients with high CRPs and those with normal CRP values; furthermore, a statistically significant reduction in hepcidin level, which is generally elevated when there's inflammation. So hepcidin levels in roxadustat are -- was shown to be reduced more than EPO. We are glad to have received this confirmatory results and to have the potential opportunity to be first to offer to CKD patients a new treatment paradigm that overcomes EPO's major drug company on hyporesponsiveness in the presence of inflammation.

Well, you might say, "Other than showing that our drug works in anemia correction, does it do anything else?" We are interested in measuring a number of clinical relevant parameters and potential benefit from roxadustat treatment. Chronic kidney disease is generally a progressive condition and CKD severity is well known to have -- to cause impact in patient's outcome and patient's quality of life, yet the treatment options for CKD is very limited and generally ineffective. A number of preclinical studies using our HIF-PHI suggests the potential benefit on the preservation of renal function. Kidney function, over time, has been routinely measured in our Phase III studies.

Preliminary results from a full analysis on patients with baseline eGFR 15 or higher in the Phase III placebo-controlled studies show that 1-year decline in eGFR in roxadustat is significantly less than placebo in CKD Stages 3 and 4 patients. We believe roxadustat treatment could offer significant clinical benefit in the non-dialysis-dependent patients by attenuating renal progression, as seen in slowing down the declines in eGFR over time. Another area that matters a lot to patients is quality of life. Fatigue and

impaired quality of life are well known complications of anemia. Improvement of quality of life with roxadustat treatment is one of our treatment objectives. In the design of our CKD Phase III program, we made good use of a large sample size of 4,300 non-dialysis patients across the 3 studies and these -- [act on] OLYMPUS to have adequate statistical power to evaluate end points for assessing these important clinical parameters. Also, the placebo comparator in the non-dialysis program serves as a solid reference for the evaluation of this potential secondary benefit of anemia therapy using roxadustat. We are excited about the preliminary results in eGFR, quality of life and other important parameters. We are targeting completion of pool analysis of these and other clinically important end points in the first half of 2019.

Turning to preliminary safety data. Results in individual studies are consistent with what one would expect in the study patient population. The integrated full safety analyses are ongoing. The adjudicated MACE results are on track for the first half of 2019. Encouraged by the robust efficacy results, the preliminary safety data in individual Phase III studies and the ongoing pool efficacy and safety analysis, we are working diligently with our partners, AstraZeneca in the preparation of NDA submission in the U.S. and with Astellas in the preparation for the MAA in Europe. Given the large amount of very rich data in these 9,000 patients, 7-study Phase III program, we are targeting U.S. submission in the third quarter and submission to EMA thereafter. In Japan, the NDA on roxadustat for treatment of anemia in dialysis-dependent CKD patients submitted by our partner, Astellas, in September 2018, is under review by PMDA.

For the treatment of -- so I'm going to turn to treatment of anemia in other conditions. For MDS patients, we have an ongoing Phase III study in transfusion-dependent lower risk MDS patients being conducted in U.S., Europe and Asia, plus another Phase II/III study in non-transfusion-dependent MDS patients in China. Each has an open label [run-in] period. Anemia in MDS is notoriously difficult to treat and we are striving to make a difference for these patients. We are encouraged by the data available in the open label portion so far. We plan to have data readout on the open label components of both MDS studies in 2019. With alignment with both partners, AstraZeneca and Astellas, we are advancing to the top-of-line portion of the U.S./European transfusion-dependent Phase III MDS study.

Last but not least, we also have support from both of our partners to start our first clinical trial in chemotherapy-induced anemia with roxadustat. This will be a Phase II study in the U.S. to start in 2019. We believe treatment of chemotherapy-induced anemia is much needed, and there is a huge unmet medical need, which we hope to make a difference in.

I'd like to now turn the call back to Tom.

Thomas B. Neff

Founder, Chairman & CEO

Thank you, Peony. Chris Chung, our Head of China Operations, will now share updates on our current activities and regulatory process. Chris, please go ahead.

Christine L. Chung

Senior Vice President of China Operations

Thank you, Tom. We had quite the exciting year-end with roxadustat receiving approval in China for CKD dialysis patients. As stated by Tom and Peony, roxadustat is now the first HIF-PHI approved anywhere in the world. In addition, this approval marks a historic milestone for China. For the first time in history, China is the first approval country for a first-in-class drug. We call this the 3 firsts.

At a macro level, the roxadustat approval is in line with the country's mission to become a global player in innovative drug development. Seeking approval in China first for a global first-in-class drug required vision and persistence on behalf of the company, our partner, AstraZeneca, and regulatory authorities in China. On behalf of the company, I would like to thank our tremendous teams in the U.S. and in China, our board and our shareholders who [are safe] in our China strategy.

The approval of non-dialysis is expected in the middle of 2019. The clinical and safety data is already reviewed as part of the dialysis approval. What largely remains is the procedural requirement of clinical site inspection, which are pending scheduling. After approval, non-dialysis will be added to the current label. To continue gathering clinical data in Chinese patients and meet a post-approval regulatory

requirement for Domestic Class 1 innovative drugs, AstraZeneca and FibroGen are planning to conduct a number of Phase IV studies, including a post-approval safety study in 2,000 patients.

With an approved drug in hand, we're now focusing on market access and commercialization plans. We anticipate commercial launch in the third quarter of 2019. There's been a significant development on the market access front since our last call. Reimbursement increases affordability for patients, and in China, this generally means entry into the National Reimbursement Drug List, or NRDL. The last time the NRDL was updated was 2017, and before that, 2009. The timing of the next NRDL update has now been confirmed, which is exciting news given that the timing has previously been uncertain. It was announced on February 19 by the National Health Commission, the Ministry of Finance and the State Medical Insurance Agency, which is the reimbursement arm of the government, that there will be a round of NRDL updates in 2019. Based on internal assessment of the opportunities, FibroGen and AstraZeneca are planning for roxadustat on being included in the group for this year.

I would like to share another update on our launch plans. AstraZeneca and FibroGen are evaluating options in early experience programs to enable access to roxadustat on a strategic basis prior to commercial launch. The dedicated roxadustat launch team, covering medical, marketing and sales, has grown from around 35 the end of 2018 to over 50 now. And we plan for this team to be close to 20 -- 200 -- apologies, 200 between FibroGen and AstraZeneca by the end of second quarter. Our commercialization partner, AstraZeneca, has launch experience, expertise and scale. The teams are highly motivated, and we're anticipating the launch with a tremendous level of excitement. We look forward to keeping you updated on our progress throughout the year.

Thank you again for your time. Tom?

Thomas B. Neff

Founder, Chairman & CEO

Thank you, Chris. I will now like to ask Dr. Elias Kouchakji to update us on clinical development activities for pancreatic cancer, idiopathic pulmonary fibrosis and muscular dystrophy in the year ahead. Elias, please go ahead.

Elias Kouchakji

Senior Vice President of Clinical Development, Drug Safety & Pharmacovigilance

Thank you, Tom. In 2018, we worked diligently on our late-stage clinical programs for pamrevlumab, which included meeting with regulators on our clinical trial protocols, KOLs, investigators in identifying clinical trial sites, identifying vendor and contracting the vendors. It's all to enable that the launch of our Phase III studies in pancreatic cancer and in IPF while keeping our DMD study on track.

Pamrevlumab is our wholly owned, first-in-class candidate that targets CTGF inhibition as an approach to treating fibrotic diseases in cancer. Targeting one of the key pathways in the fibrosis process, pamrevlumab has demonstrated the potential to address a critical aspect of how each of these diseases progress. To date, more than 600 patients have been treated with pamrevlumab with some patient having been treated for up to 5 years, and pamrevlumab has been well tolerated across a range of doses with no dose-limiting toxicity identified.

In locally advanced pancreatic cancer, we are in the process of initiating a multinational, randomized, double-blind, placebo-controlled Phase III study that will evaluate neoadjuvant pamrevlumab therapy in combination with gemcitabine and nab-paclitaxel. We will be enrolling approximately 260 patients in this study. The design of this study is similar to our Phase II trials, and we will assess in this study resectability and resection and overall survival. Should the resection rate favor the pamrevlumab combination, we will be requesting a meeting with the FDA to discuss a marketing application under the provisions of accelerated approval.

Turning to pamrevlumab for IPF. In the second quarter, we will initiate randomization in a multinational, double-blind, placebo-controlled Phase III study evaluating a population of patient who are not currently receiving approved therapy. We will plan to enroll approximately 500 patients. The primary end point for this trial will be change in percent predicted FVC from baseline.

Moving to our ongoing Phase II study in Duchenne muscular dystrophy non-ambulatory patient. We are on target for all patient to complete 1 year of therapy in March of this year and assessment thereafter. Some of these patients have completed 2 years of treatment and will be started on their third year. And another group has completed 3 years of therapy and already started on their fourth year of pamrevlumab treatment.

With pamrevlumab, we believe we have the potential to develop an entirely new therapeutic option for diseases that are progressive, debilitating and fatal. We are looking forward to updating you on pamrevlumab progress in these 3 indication.

Thank you for your time today, and I will turn the call back to Tom.

Thomas B. Neff

Founder, Chairman & CEO

Thank you, Elias. Pat Cotroneo, our Chief Financial Officer, will now discuss financial highlights for the fourth quarter and full year. Pat, could you please go ahead?

Pat Cotroneo

Senior VP of Finance & CFO

Thank you, Tom. As announced today, total revenue for the quarter ended December 31, 2018, was \$108.1 million as compared to \$30.7 million for the fourth quarter of 2017. For the same period, operating expenses were \$88.1 million and net income was \$21 million or \$0.25 per basic share and \$0.23 per diluted share; as compared to operating expenses of \$66.3 million, a net loss of \$33.9 million or \$0.41 per basic and diluted share for the fourth quarter last year. Included in operating expenses for the quarter ended December 31, 2018, was an aggregate noncash portion totaling \$15 million, of which \$13.7 million was a result of stock-based compensation expense as compared to an aggregate noncash portion totaling \$11.8 million, of which \$9.9 million was the result of stock-based compensation expense for the same period in the prior year.

We noted a few nonrecurring items pertaining to revenue, which reduced our 2018 burn and resulted in net profit in the fourth quarter: the first, approximately \$44 million in roxadustat API shipment to Astellas to be used for product validation work and ultimately, commercial sale, which represents a second shipment in 2018 totaling \$64.8 million; and the second, China approval-related milestones totaling \$12 million.

Total revenue for the year ended December 31, 2018, was \$213 million, of which \$148.2 million pertains to license and development revenue from our partners. For the same period, operating expenses were \$299.7 million or \$182 million net of partner reimbursement, and net loss was \$86.4 million or \$1.03 per basic and diluted share. Included in operating expenses for the year ended December 31, 2018, was an aggregate noncash portion totaling \$58.7 million, of which \$52.1 million was a result of stock-based compensation expense.

At December 31, 2018, FibroGen had \$747.2 million in cash, restricted time deposits, cash equivalents, investments and receivables. For the full year 2019, we are currently projecting a year-end cash balance in the range of \$720 million to \$730 million. Our judgment is that roxadustat NDA and MAA will be filed this year, and this range, therefore, includes approximately \$192.5 million in anticipated milestone payments, of which the vast majority are associated with these filings.

Thank you. And I will like now to turn the call back over to Tom.

Thomas B. Neff

Founder, Chairman & CEO

Thank you, Pat. 2019 will be a busy and exciting year for roxadustat and pamrevlumab across multiple highly promising therapeutic indications.

Starting with roxadustat in 2019. We expect to have completed the adjudication for MACE analysis to support the NDA and MAA submissions in the second quarter of 2019. Following that, we plan to submit

our U.S. NDA for the treatment of anemia and dialysis-dependent and non-dialysis-dependent CKD to the FDA in the third quarter of 2019. In Europe, we anticipate our partner, Astellas, will submit an MAA for dialysis-dependent and non-dialysis-dependent CKD after the submission of our U.S. NDA. In China, we are also expecting to add non-dialysis-dependent CKD patients to the roxadustat label and then scheduling and completion of CFDI inspection of Study 808 trial sites in the first half of 2019. In Japan, we expect a decision on NDA approval for roxadustat in dialysis-dependent CKD in the second half of 2019. In MDS, we expect to advance roxadustat in a double-blind, placebo-controlled portion of the U.S./EU Phase III study with chemotherapy-induced anemia. We expect to start enrolling patients in our Phase II in the U.S. in 2019.

For pamrevlumab, our first-in-class anti-fibrotic candidate, our multinational, randomized, double-blind, placebo-controlled Phase III study in LAPC evaluating neoadjuvant pamrevlumab therapy in combination with gemcitabine and nab-paclitaxel will be underway. We expect to commence the pivotal multinational, randomized, double-blind, placebo-controlled Phase III study in IPF in the second quarter of 2019. Next quarter, we also look forward to reporting top line results from our Phase II muscular dystrophy study in non-ambulatory juveniles, including what we expect to be notable data from our pulmonary function test, measured by percent predicted FVC, cardiac function measured by left ventricular ejection fraction measured with MRI, and muscle strength tests.

With that, I'd like to turn this call back over to Karen for Q&A. Karen, please?

Karen L. Bergman

Vice President of Investor Relations & Corporate Communications

Thank you, Tom. And I'd like to thank everyone for your patience today while we are experiencing a little technical difficulty in starting the call. Let's open the call now with questions moderated by Tom Neff. Thank you.

Question and Answer

Operator

[Operator Instructions] And our first question comes from Michael Yee from Jefferies.

Michael Jonathan Yee

Jefferies LLC, Research Division

My question relates to roxa and what are the gating steps at this point to finishing up the final MACE analysis, which I guess you said would be in the second quarter. Where are you with that? How will it be reported out? And my second part of that question is as it relates to both the dialysis and non-dialysis readouts, how important is delay in progression of eGFR as well as the hyporesponder population? How important are those populations given your confidence in the readout? And will you be able to comment about those?

Thomas B. Neff

Founder, Chairman & CEO

Thank you, Michael. So I think the second part of this question, I'm going to divide it into a couple sets of comments. We are not dependent on hyporesponse or progression results as it relates to the filing post adjudication for this year's NDA submission. However, we do have the data and we're very, very interested in that data. Peony, would you like to add anything about progression for CKD or hyporesponse patients? Will you, please?

K. Peony Yu

Chief Medical Officer

Yes. Thanks, Tom. Yes, so we find that in terms of the progression slowing down, the decline in eGFR has been viewed as very important for -- when we speak of -- with our KOLs and our patients. And then for -- and we know that the hyporesponse has always been the Achilles' heel for EPO therapy, and it causes patients not able to achieve the hemoglobin that they wanted -- level they want to be. So this is -- and then to try to get there to the target hemoglobin, historically, too much EPO then would end up be given to the patient, and then that results in safety issues. So having a drug that -- with a dose requirement and effectiveness not impacted by inflammatory status has been viewed as a very positive characteristic for both efficacy and safety of evaluation. And this is also important in our discussion with CMS. So these are just 2 example of some of the potential benefits that we find with roxadustat therapy. We believe that FDA will look -- they evaluate the drug -- they evaluate based on the benefit-risk ratio, and these are incremental to our articulation of the value of roxadustat.

Thomas B. Neff

Founder, Chairman & CEO

Thank you, Peony. Mike, the other part of your question. We have an adjudication pool in the U.S. and we have another one slightly different in Europe. So the objectives are to get those adjudication pools completed. We will be, of course, working with our partners in both cases. So I think in dialysis, where there's been many studies before, it's pretty clear how to go forward and we'll try our best to make the assessment very -- as clear as possible. In non-dialysis, it's important to note that, that -- this treatment population where you have CKD patients not being treated with anemia therapy and they're starting a study at hemoglobin 9 or 9.5. This is a completely new treatment circumstance. And for instance, one of the things that we saw in this study very clearly was the placebo arm was very sick and frequently dropped early. And so we are, of course, evaluating all that stuff but it's a much more complex analysis, and I think the idea here is we will do the best we can to update it in a manner where we can sort of see where we're going and what the sentiment is. Thank you for the questions.

Operator

And our next question comes from Adam Walsh with Stifel.

Adam Anderson Walsh

Stifel, Nicolaus & Company, Incorporated, Research Division

I've got a quick one for Peony and then one for Tom as well, if that's okay. Peony, on the non-dialysis CKD roxa results where you have preservation of kidney function as measured by eGFR, that's obviously a very profound result with the potential implications and maybe preserved kidney function and delayed dialysis in these non-dialysis-dependent patients. How much do you think you can leverage that in the clinical community? And how would you go about doing that should you receive approval for roxa in that setting? And then Tom, very quickly, you have a ton going on inside the company right now with a lot of, obviously, initiatives. Do you feel that you're adequately staffed and resourced to execute on the ongoing and planned trials in timely manner as well as the worldwide approval potentially and launch of roxa?

K. Peony Yu

Chief Medical Officer

Andrew (sic) [Adam], thank you so much for a very good question. There has been -- we believe that the kidney deserves to have enough oxygen and also deserves to have the benefit of the protective function from a HIF-PHI. And being able to see preservation of kidney function has been something that I and my team have been dreaming for the day when we designed the Phase III program. So now we are happy about it and the -- every single nephrologist that had provided an opinion to me about this tells me it will be valuable to be able to show this benefit, but I will take your questions and advice. And while we are preparing our NDA, we will do our best to articulate this and have some good practice by the time we have to talk to more clinician in the future.

Thomas B. Neff

Founder, Chairman & CEO

So, Adam, with respect to your question to me, adequate resourcing, first off, thankfully, we have been with adequate financial resources, which makes a lot of other things possible, and we expect that to continue for a while. As I look at the anemia program in China, we have the second largest company selling drugs in China, AstraZeneca, as our partner in the launch. They are a fantastic operation in China. This year's revenues in that business were nearly \$4 billion, about 25% up year-on-year, so a lot of momentum. And so we feel like we have excellent resourcing for CKD anemia. In Japan, our partner is Astellas -- originally, it was Yamanouchi. And then after the merger with Fujisawa, it became Astellas. And we think we have a great partner in Japan. They're excellent at execution and so on. And so again, you're looking at very big companies with long-time commitment to these programs, focused on these activities for 8 or 9 years. And so I think we're in pretty good shape to those places. In Europe -- and now we're getting into the areas where the regulatory story is still in front of us a little bit. We have to find out what's going to happen, but I would say that in Europe, we have Astellas as a partner. In the U.S., we have AstraZeneca as a partner. And in both cases, we have very motivated leadership, very motivated teams who have excelled in their work for 8, 9 years in the case of Astellas and about 6 years in the case of AZ that we've been able to observe. And so in all of these cases, we are holding royalty rights, not being directly responsible on the ground. Things can happen, of course. And as we expand CKD activities into other areas of anemia, we have to calibrate adequate amount of resourcing at every step. With the antibody, you've got programs that are right at proof of concept stage. And in each area, they're monumental proof of concepts. They happen because there's been no treatments previously. In the case of both DMD and pancreatic cancer, it's just that simple. There's not been treatments previously. And so for us, we have to decide in a wise way how to allocate rights and markets around the world with potential partners and so on, but again, we think we're in pretty good shape in this regard. So let me stop there.

Operator

And the next question comes from Geoffrey Porges from Leerink.

Geoffrey Craig Porges

SVB Leerink LLC, Research Division

Just a couple of detailed questions on things that you mentioned on the call. First question, you mentioned the NRDL new listings in 2019. Could you talk about how logistically that might affect your launch for roxa

in China? Do you intend to wait to see what that list is and launch with that price or will you launch with a commercial price and then potentially have a low price with the NRDL listing? And then secondly, I think you mentioned AstraZeneca doing a 2,000-patient post-approval study, I think. Could you give us some details about that? And then lastly, I apologize for all the questions, but on the Duchenne's disclosure, could you give us a sense of what you'll be able to disclose to us and then what you'll sort of say so we should calibrate our expectations for what to hear from that announcement when it comes?

Thomas B. Neff

Founder, Chairman & CEO

So let me parse this out there. The Duchenne's, I'll have Elias address that. Chris, take on the first part, NRDL. And then we'll deal with the second part. So just go ahead.

Christine L. Chung

Senior Vice President of China Operations

Sure. Geoff, with regard to your first question, do we plan to wait until NRDL or clarity around pricing of NRDL before launch, the answer is no. Those 2 are separate ideas. We will launch when we're ready to launch. We will submit an application for NRDL. As you know, the timing -- even though we know it's 2019, the exact timing is uncertain. While we're very optimistic that roxadustat is going to be considered, the criteria is uncertain. And while we're very optimistic that we have a value proposition to demand -- or command, rather, a very valuable pricing for roxadustat, that is also subject to negotiations. So currently, the plan is to unlink the 2.

Thomas B. Neff

Founder, Chairman & CEO

So Geoff, with regard to the PAS study, let me point out that when I first went to China to negotiate the idea of an oral therapy, which was well beyond a decade ago, we understood the system we would be administered under was one where pathway to first approval was a little more rapid than it might be in the West, but there was a post-approval study, or PAS, post-approval safety study, that was required -- mandatory requirement for final approval and the extension of administrative exclusivity for a longer period of time. And so that PAS study is what I think you're asking about. And Chris, go ahead and address the question, please.

Christine L. Chung

Senior Vice President of China Operations

Sure. So the post-approval safety commitment is a regulatory requirement for Domestic Class 1 innovative drug, is not specific to roxadustat. Peony and Elias are both here, and we have met with the regulatory authorities in terms of expectations. As far as I know, it's a very routine post-approval safety study with a minimum of 2,000 patients, and I did not get the sense that there's anything specifically to roxadustat or anything that is funky about it. And to clarify the party who's going to run the study is FibroGen, is not AstraZeneca.

Thomas B. Neff

Founder, Chairman & CEO

So Elias, please look after muscular dystrophy and explain what we are hoping for here.

Elias Kouchakji

Senior Vice President of Clinical Development, Drug Safety & Pharmacovigilance

So as Tom mentioned before, let's just say with our patient is completing 1 year of treatment in the mid of March, we still have to clean the data, but we are looking at this key function, looking at the muscle test and the pinch and the pull and others. And at the same time, we are doing an MRI. Similarly, we're doing ejection fraction, left ventricular ejection fraction. And similarly, we have MRIs for the heart. We're doing cardiac MRI. And the pulmonary functions, we are testing for the FVC percent predicted. We will await until the data is completed, until the last patient is enrolled, transfer the data, clean the data. We will be looking at this data at that time. And then when we will -- after we see the data completely, we will

make an internal decision, how -- and the evaluation of the data, what is our strategy will be for Duchenne muscular dystrophy. We are hoping that this will be a good and positive data that is -- provide a very new option for this patient. And as I mentioned, we have patient now who started on their fourth year of therapy. So that is -- by itself, is giving us hope.

Operator

And our next question comes from Joel Beatty from Citi.

Joel Lawrence Beatty

Citigroup Inc, Research Division

I guess can you discuss what are the most important end point roxadustat program that clinicians will care about for use and prescribing in the non-dialysis on an anemia setting?

Thomas B. Neff

Founder, Chairman & CEO

Okay. Joel, I think -- maybe I'll try to answer this question. In non-dialysis setting, if it is the case, there are patients that are relatively well, meaning eGFR is a baseline of 20 to 30. We're very hopeful we see evidence that we can either slow progression or stall progression in those kinds of patients, as measured by eGFR over time. And of course, this idea would then lead to the notion that patients that are aware of their emerging renal disease and aware of what dialysis is all about might be very motivated to address use of roxa as a chronic therapy that slows down or avoids a progressive disease outcome. It's something akin to anti-cholesterol medicine. So that -- in that kind of setting, that's what you would hope for. With patients that are sicker, you get in situations where they're actually losing more and more oxygen capacity in their organs, and so it's an all-out alert and a multiplier on all kinds of other diseases. And so I think if it's a safe and effective medicine that you can routinely with once-a-week dosing perhaps have level hemoglobin, 11 or something like that, that kind of idea, you may forestall numerous kinds of cardiovascular, pulmonary system and functional issues that are well documented in other categories of medicine. So that's how we look at it. Thank you for the question.

Joel Lawrence Beatty

Citigroup Inc, Research Division

Great. And if I can ask another question. Can you discuss the definition of non-inferiority that will be used for the MACE analysis?

Thomas B. Neff

Founder, Chairman & CEO

Where, in what jurisdiction?

Karen L. Bergman

Vice President of Investor Relations & Corporate Communications

Joel, did you hear Tom's follow-on question? This is Karen.

Joel Lawrence Beatty

Citigroup Inc, Research Division

Oh, sorry. What was that?

Karen L. Bergman

Vice President of Investor Relations & Corporate Communications

He asked in which -- or in what jurisdiction are you inquiring.

Joel Lawrence Beatty

Citigroup Inc, Research Division

Sure. So I guess let's say for the FDA approval, there'll be the 2 pools that -- from my understanding, FDA will look at non-dialysis and dialysis and I'm curious on what definition could be used.

Thomas B. Neff

Founder, Chairman & CEO

So Peony, do you want to take on that U.S. ROW program?

K. Peony Yu

Chief Medical Officer

Sure. So the -- and we are now in discussion with the FDA. So we'll use the adjudicated results and it will be based on MACE, which is based on the composite of death, MI, stroke and it will -- the count will be the number of patients who have one or more of these events. And then the reason Tom had mentioned -- asked what jurisdictions are in Europe, we'll be looking at MACE plus. So that will be death, MI, stroke, hospitalization due to heart failure and hospitalization due to unstable angina.

Thomas B. Neff

Founder, Chairman & CEO

And the [indiscernible]

K. Peony Yu

Chief Medical Officer

Yes. So -- and then the criteria for evaluations are -- also differ in the 2 jurisdictions and we -- yes. And then we -- so we are still completing the adjudication, and then the step after that will be to -- for analysis of such -- of those data. Go ahead, please.

Thomas B. Neff

Founder, Chairman & CEO

Yes, anything else?

Joel Lawrence Beatty

Citigroup Inc, Research Division

No, sir.

Thomas B. Neff

Founder, Chairman & CEO

Thank you, Peony. Anything else?

Joel Lawrence Beatty

Citigroup Inc, Research Division

No.

Operator

And we have another question from Andy Hsieh with William Blair.

Tsan-Yu Hsieh

William Blair & Company L.L.C., Research Division

One is for Chris. I think you mentioned about -- like a special early access program. From a modeling perspective, are -- is the company along with AstraZeneca thinking about addressing maybe the private pay population? And could you just provide more details regarding that?

Thomas B. Neff

Founder, Chairman & CEO

So Andy, let me prelim this a little bit. In China, the prescriber utilization profile matters for the NRDL negotiations. So this is not really into private pay, although it may be a side benefit. Chris, do you want to go ahead and...

Christine L. Chung

Senior Vice President of China Operations

Sure. Andy, thank you for your question. So I confirm what Tom just said. The early access program is really addressed at market access. As you can imagine, roxadustat is being first launched in China with a 450-subject data set, and the next approval won't be until the second half of this year in Japan. So we're really focused for market access purposes on expanding prescriber experience because we have no referenceable data from outside of China and we have not started any of the Phase IV studies. So in order to get into the reimbursement list and in order to get into the formulary at 5,000 target hospitals, we need people to have used this drug. And in terms of early access programs, the typical 3 types are we could either donate the drug for free or we could give away commercial samples, again, for free; or we could do a patient assistance program, which is basically a subsidy program where we book a bit of our revenues and we give part of the dosing regimen away for free. We are actively working with AstraZeneca to evaluate the pros and cons of each of those 3 paradigms as well as if there's a hybrid that might serve us well in this situation, but it's really not for private pay. I can really focus on market access to enhance our chances of market success.

Thomas B. Neff

Founder, Chairman & CEO

The other point I'd make sure is that the first step, this spring, we will focus on the area around Beijing and very carefully evaluating how to move forward. And in the second step, the full-blown machinery of AstraZeneca kicks in, and they have really extensive distribution in China. The last I heard is 13,000 salespeople. And so there's ways to pick up the speed very fast once we decide on the pathway we're taking, which is the virtue of partnering with someone. It has been as successful as AstraZeneca. Anyway, thank you for the question.

Tsan-Yu Hsieh

William Blair & Company L.L.C., Research Division

Sure. Do you mind if I ask another one? So just the clarification for -- this is a question for Elias, about the MDS Phase III study for roxadustat. Can you kind of remind us what the open label transitioning to the randomized portion entails? Is there -- so what kind of -- what's the rationale behind the open label phase?

Thomas B. Neff

Founder, Chairman & CEO

Yes. So let me help a little bit. In MDS, we have 2 distinct programs. One was in the U.S. The end point is transfusion, free for 8 weeks or longer, which is a pretty tough standard actually. And outside of the U.S., in the China program, we're looking at patients that are [really] naive for therapies, as such hemoglobin increase. And there, anything more than 1.5 of hemoglobin catches an end point but it's very different. And so what we're talking about today -- and I'll turn this over to Peony now, is in MDS in the U.S., we now have gotten to the point where there's enough data that our partners in AstraZeneca are saying gee whiz -- there's a lot of patients here that have gone beyond the 8 weeks of transfusion free. Let's get going on the double-blind study. So Peony, please explain.

K. Peony Yu

Chief Medical Officer

Yes. So for the U.S. study, before we start that study, we met with the FDA, and the understanding was that we will be pursuing this study in the -- for patients who are transfusion-dependent and demonstrate transfusion independence for 8 weeks. So now that we have -- we are -- we have looked at the openlabel data and very much encouraged by that and have gone over the data with our partners, we are at the point of starting to randomize into the double-blinded portion, which has a -- it's planned for having

160 patients with a 3 to 2 randomization. Now separately -- so in China, because there is such severe shortage of blood for transfusion, it is much more practical to study MDS patients with roxadustat by taking patients who are anemic and treat them with roxa to see if we could increase the hemoglobin level because in China, the hemoglobin threshold for physicians to even start thinking about ordering blood for transfusion is below 6. And most -- there are many patients who may -- MDS patients may walk around with hemoglobin below that level and still do not get to have a blood transfusion, which is a different situation than U.S., where the transfusion threshold is more around 8 also. And together, with the result of this study, we believe that we will have a very good basis to cover the entire spectrum of a lower-risk MDS anemic need. Do you have any questions?

Tsan-Yu Hsieh

William Blair & Company L.L.C., Research Division

No, I think that is a great explanation.

Operator

And our next question comes from Difei Yang from Mizuho Securities.

Difei Yang

Mizuho Securities USA LLC, Research Division

Just a couple. The first question is around -- I'm wondering if you could shed some light on how you think about pricing for roxadustat in China and how would that be relative to the U.S. and Japan pricing.

Thomas B. Neff

Founder, Chairman & CEO

Chris, why don't you go ahead with that one, please?

Christine L. Chung

Senior Vice President of China Operations

Sure. Thank you for the question specifically about pricing in China. So one thing, based on AstraZeneca's experience, we are very careful about is the referenceability of the China pricing, with this new business model. China is launching first before the rest of the world. And to date, we believe that China pricing will not, in any way, affect the U.S., Europe or Japan pricing. It is also a foundational, strategic decision by Tom originally and FibroGen that this is a Domestic Class 1 drug and their approval is not referencing the [global] drug. So it's very difficult to make the case that U.S. data was used to get approval in China. So the current assumption is these 2 are linked. In terms of the pricing level in China, we've conducted extensive pricing studies in China with potential prescribers, potential self-pay patients, potential patients who had received reimbursement as well as proxies to the reimbursement agency to understand a couple of factors. One is what is the fundamental value proposition of roxadustat relative to ESAs, which we believe is very strong. The second is the affordability of the Chinese government to cover roxadustat if we reimbursed for dialysis and we expect a much larger non-dialysis population that was previously not addressable by ESAs. Third is the affordability of the self-pay portion by the patients who choose to use HIF-PHIs and is reimbursed. So the combination of those factors, that will be taken into consideration. And finally, as we could all see, because of the expansion of access to innovative drugs, innovative drugs are being widely reimbursed, but there are also price cuts that are quite significant that were levied in particular with oncology drugs in 2018. So at the end of the day, it's really what sells and what we can get reimbursed for, and those decisions are yet to be made but the methodology is as I just described.

Thomas B. Neff

Founder, Chairman & CEO

Difei, do you want to ask more questions, please?

Difei Yang

Mizuho Securities USA LLC, Research Division

Yes. Thank you for that detailed explanation. So we have been observing, for example, for PD-1 agents, roughly the China pricing is 50% of that -- of the U.S. pricing. Is that the ballpark we should be thinking about?

Thomas B. Neff

Founder, Chairman & CEO

This is, unfortunately, a little bit complicated. So let me try how I would think about it. In the U.S. and in Europe, you might have dialysis reimbursement these days, maybe \$3,000 or \$4,000 per patient per year for these anemia therapies and normal government-reimbursement-type program. And that, of course -implicitly, that's a TIW schedule dosing. So dialysis exchange matches the time the drug goes onboard with the patient. With our drug, we don't have a constraint of TIW or BIW. We can do QW. And so one of the interesting parts for Chinese counterparties and the government looking at reimbursement is that we can talk about dialysis at TIW. We can also talk about QW at much lower prices if we price on units by milligrams. And as a result, we have some flexibility to deal with the biggest challenge in China, which is to have prices that are reasonably affordable by people other than the top 10% by wealth in society. And so I think that we have flexibility that's different than might have happened in other situations. In addition, we have aspects of the HIF biology that address things that are way, way different than EPO, for sure, but they -- also, the HIF biology addresses risk factors. I've seen a study from UCLA where 11 identifiable EPO risk factors all are -- somehow are negated or nullified with the HIF therapies, that kind of idea. And so how those things get priced is a part of the conversation that's still in front of us. But without a doubt, these things are valuable. And so what I would say my challenge in China is to make sure that governments -- I feel like we're dealing with them in a fair way and we're not being extortionate about pricing, and I'm pretty confident we can do that and still make this thing work, right. So still...

Difei Yang

Mizuho Securities USA LLC, Research Division

Then turning the pricing discussion into the U.S., do you think roxadustat will be in the bundle or out of the bundle?

Thomas B. Neff

Founder, Chairman & CEO

This question, I think, is dependent on future conversations. We have incident dialysis data that we debated whether to talk about on this call or just wait until we get through the whole process. We decided to wait just to be careful, but that kind of data is what CMS, several years ago, told us was what they wanted to see to make some decisions here. And at the time we talked to them, the proffer of possibly being entirely outside the bundle because it's new technology, outside regulation hasn't been achieved before and so on. I think that we wait now to understand better U.S. government position, which is obviously evolving, too, and how they're going to look at things. But the most simple and straightforward way to think about this is the different technology and you'd like to see outcome differences in treatment that are clear-cut. And if we can show that, I think that it's game on. And if you can't show it, it's sort of ridiculous to expect to be outside the book, right? So I think we like our chances here, but we have to wait a few more weeks to get to the point we can talk about it articulately with quantitative presentation, if you follow what I mean.

Difei Yang

Mizuho Securities USA LLC, Research Division

Yes, yes. That makes perfect sense.

Operator

And that concludes our question-and-answer session. I'll turn the call back over to Tom Neff for closing comments.

Thomas B. Neff

Founder, Chairman & CEO

To those that are still on the call, thank you for joining today. I'm sorry we started late. 2018 was a remarkable year for FibroGen in that we advanced the development of 2 promising products, each with multiple significant market opportunities now closer to patients who need new and innovative treatment options. We announced the approval of roxadustat in China just days apart from reporting our U.S. Phase III efficacy data. These are -- both of these programs are nearly a decade long effort, enormous amount of commitment. And I can only, in the most humble way, say I appreciate everyone involved that supports us because it's so impossible to imagine having the chance to do that kind of work for such a long period of time and still be here to see the outcomes. The dedication and commitment of our employees are really astounding. And in the case of pamrevlumab, we've gotten now to the point of FDA agreeing on protocols for Phase III and we're in the contracting and execution mode of doing the Phase IIIs. We also will begin to see the promise of anti-CTGF therapy or pamrevlumab therapy in muscular dystrophy and, in particular, impact on ejection -- cardiac ejection fraction and on cardiopulmonary measurements where the situation is desperate almost from the day the boys go into wheelchairs. So we're very, very interested in what the potential is there or hope for those patients.

Our company has maintained its financial discipline. So we are able to do this stuff without being in a fire sale situation, and thanks to the gods, it hasn't been that way so far. Obviously, it's always delicate in a biotech company, but right now, we're okay. I would like to take the time here to thank every member of the FibroGen team all over the world for invaluable contributions as well as the physician and investigators who participated in our Phase III programs in anemia as well as our collaboration partners and our investors for continued, awesome support. We look forward to keeping you updated on our progress through 2019. I'd like to wish everyone a good afternoon and good evening. Thank you all for being with us today here.

Operator

Thank you, ladies and gentlemen. This concludes today's conference. Thank you for participating and you may now disconnect.

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EXHIBIT H

UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

(Ma		

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2018

OR

TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT **OF 1934**

> For the transition period from to. Commission file number: 001-36740

FIBROGEN, INC.

(Exact name of registrant as specified in its charter)

Delaware

(State or other jurisdiction of incorporation or organization)

77-0357827 (I.R.S. Employer Identification No.)

409 Illinois Street San Francisco, CA

94158

(Address of principal executive offices)

(zip code)

Registrant's telephone number, including area code:

(415) 978-1200

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class Common Stock, \$0.01 par value Name of Exchange on Which Registered The NASDAQ Global Select Market

Securities registered pursuant to Section 12(g) of the Act:

None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes 🗷 No 🗆

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes \square No \square

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ✓ No □

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes 🗸 No 🗆

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. 🗸

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act:

Ø Large accelerated filer П Non-accelerated filer Smaller reporting company Emerging growth company П

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. \square

Indicate by check mark whether the registrant is a shell company (as defined in Exchange Act Rule 12b-2). Yes \square No \square

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant, computed by reference to the closing price as of the last business day of the registrant's most recently completed second fiscal quarter, June 30, 2018, was approximately \$3,548.1 million. Shares of Common Stock held by each executive officer and director and stockholders known by the registrant to own 10% or more of the outstanding stock based on public filings and other information known to the registrant have been excluded since such persons may be deemed affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

The number of shares of common stock outstanding as of January 31, 2019 was 85,562,391.

DOCUMENTS INCORPORATED BY REFERENCE

Items 10, 11, 12, 13 and 14 of Part III of this Annual Report on Form 10-K incorporate information by reference from the definitive proxy statement for the registrant's 2019 Annual Meeting of Stockholders to be filed with the Securities and Exchange Commission pursuant to Regulation 14A not later than after 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K.

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FORWARD-LOOKING STATEMENTS

This Annual Report filed on Form 10-K and the information incorporated herein by reference, particularly in the sections captioned "Risk Factors," "Management's Discussion and Analysis of Financial Condition and Results of Operations" and "Business," contains forwardlooking statements, which involve substantial risks and uncertainties. In this Annual Report, all statements other than statements of historical or present facts contained in this Annual Report, including statements regarding our future financial condition, business strategy and plans and objectives of management for future operations, are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "believe," "will," "may," "estimate," "continue," "anticipate," "contemplate," "intend," "target," "project," "should," "plan," "expect," "predict," "could," "potentially" or the negative of these terms or other similar terms or expressions that concern our expectations, strategy, plans or intentions. Forward-looking statements appear in a number of places throughout this Annual Report and include statements regarding our intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things, our ongoing and planned preclinical development and clinical trials, the timing of and our ability to make regulatory filings and obtain and maintain regulatory approvals for roxadustat, pamrevlumab and our other product candidates, our intellectual property position, the potential safety, efficacy, reimbursement, convenience clinical and pharmaco-economic benefits of our product candidates, the potential markets for any of our product candidates, our ability to develop commercial functions, our ability to operate in China, expectations regarding clinical trial data, our results of operations, cash needs, spending of the proceeds from our initial public offering and the concurrent private placement, financial condition, liquidity, prospects, growth and strategies, the industry in which we operate and the trends that may affect the industry or us. We have based these forward-looking statements largely on our current expectations and projections about future events and financial trends that we believe may affect our financial condition, results of operations, business strategy and financial needs. These forward-looking statements are subject to a number of risks, uncertainties and assumptions described in the section of this Annual Report captioned "Risk Factors" and elsewhere in this Annual Report.

These risks are not exhaustive. Other sections of this Annual Report may include additional factors that could adversely impact our business and financial performance. Moreover, we operate in a very competitive and rapidly changing environment. New risk factors emerge from time to time, and it is not possible for our management to predict all risk factors nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements.

You should not rely upon forward-looking statements as predictions of future events. We cannot assure you that the events and circumstances reflected in the forward-looking statements will be achieved or occur. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements. The forward-looking statements made in this Annual Report are based on circumstances as of the date on which the statements are made. Except as required by law, we undertake no obligation to update publicly any forward-looking statements for any reason after the date of this Annual Report or to conform these statements to actual results or to changes in our expectations.

This Annual Report also contains market data, research, industry forecasts and other similar information obtained from or based on industry reports and publications, including information concerning our industry, our business, and the potential markets for our product candidates, including data regarding the estimated size and patient populations of those and related markets, their projected growth rates and the incidence of certain medical conditions, as well as physician and patient practices within the related markets. Such data and information involve a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates.

You should read this Annual Report with the understanding that our actual future results, levels of activity, performance and achievements may be materially different from what we expect. We qualify all of our forward-looking statements by these cautionary statements.

ITEM 1A. RISK FACTORS

Investing in our common stock involves a high degree of risk. You should carefully consider the risks described below in addition to the other information included or incorporated by reference in this Annual Report on Form 10-K, including our consolidated financial statements and the related notes and "Management's Discussion and Analysis of Financial Condition and Results of Operations," before deciding whether to invest in our common stock. The occurrence of any of the events or developments described below could harm our business, financial condition, results of operations and growth prospects. In such an event, the market price of our common stock could decline, and you may lose all or part of your investment. Although we have discussed all known material risks, the risks described below are not the only ones that we may face. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also impair our business operations.

Risks Related to Our Financial Condition and History of Operating Losses

We have incurred significant losses since our inception and anticipate that we will continue to incur losses for the foreseeable future and may never achieve or sustain profitability. We may require additional financings in order to fund our operations.

We are a clinical-stage biopharmaceutical company with two lead product candidates in clinical development, roxadustat in anemia in chronic kidney disease ("CKD") and myelodysplastic syndromes ("MDS"), and pamrevlumab (FG-3019) in idiopathic pulmonary fibrosis ("IPF"), pancreatic cancer and Duchenne muscular dystrophy ("DMD"). Pharmaceutical product development is a highly risky undertaking. To date, we have focused our efforts and most of our resources on hypoxia-inducible factor ("HIF") and fibrosis biology research, as well as developing our lead product candidates. We are not profitable and, other than in 2006 and 2007 due to income received from our Astellas Pharma Inc. ("Astellas") collaboration, have incurred losses each year since our inception. We have not generated any revenue based on commercial drug product sales to date. We continue to incur significant research and development and other expenses related to our ongoing operations. Our net loss for the year ended December 31, 2018 was approximately \$86.4 million, and our net loss for the years ended December 31, 2017, and 2016, recast from amounts previously reported due to the adoption of the new revenue standards, were approximately \$120.9 million and \$58.1 million, respectively. As of December 31, 2018, we had an accumulated deficit of \$715.8 million. As of December 31, 2018, we had capital resources consisting of cash, cash equivalents and short-term investments of \$621.4 million plus \$55.8 million of long-term investments classified as available for sale securities. Despite contractual development and cost coverage commitments from our collaboration partners, AstraZeneca AB ("AstraZeneca") and Astellas, and the potential to receive milestone and other payments from these partners, and despite our expectation to launch commercialization efforts in China for roxadustat for the treatment of anemia caused by CKD in dialysis patients, we anticipate we will continue to incur losses for the foreseeable future, and we anticipate these losses will increase as we continue our development of and seek regulatory approval for our product candidates and in our commercialization efforts. If we do not successfully develop and obtain regulatory approval for our existing or any future product candidates and effectively manufacture, market and sell any product candidates that are approved, we may never generate product sales, and even if we do generate product sales, we may never achieve or sustain profitability on a quarterly or annual basis. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our stockholders' equity and working capital. Our failure to become and remain profitable would depress the market price of our common stock and could impair our ability to raise capital, expand our business, diversify our product offerings or continue our operations.

We believe that we will continue to expend substantial resources for the foreseeable future as we continue late-stage clinical development of roxadustat, grow our operations in the People's Republic of China ("China"), expand our clinical development efforts on pamrevlumab, seek regulatory approval, prepare for the commercialization of our product candidates, and pursue additional indications. These expenditures will include costs associated with research and development, conducting preclinical trials and clinical trials, obtaining regulatory approvals in various jurisdictions, and manufacturing and supplying products and product candidates for ourselves and our partners. In particular, in our planned Phase 3 clinical trial program for roxadustat, which we believe will be the largest Phase 3 program ever conducted for an anemia product candidate, we are expecting to enroll more than 8,000 patients for our U.S. and European programs alone. We are conducting this Phase 3 program in conjunction with Astellas and AstraZeneca, and we are substantially dependent on Astellas and AstraZeneca for the funding of this large program. The outcome of any clinical trial and/or regulatory approval process is highly uncertain and we are unable to fully estimate the actual costs necessary to successfully complete the development and regulatory approval process for our compounds in development and any future product candidates. We believe that the net proceeds from our 2017 public offerings, our existing cash and cash equivalents, short-term and long-term investments and accounts receivable, and expected third party collaboration revenues will allow us to fund our operating plans through at least the next 12 months. Our operating plans or third party collaborations may change as a result of many factors, which are discussed in more detail below, and other factors that may not currently be known to us, and we therefore may need to seek additional funds sooner than planned, through offerings of public or private securities, debt financings or other sources, such as royalty monetization or other structured financings. Such financings may result in dilution to stockholders, imposition of debt covenants and repayment obligations, or other restrictions that may adversely affect our business. We may also seek additional capital due to favorable market conditions or strategic considerations even if we currently believe that we have sufficient funds for our current or future operating plans.

Our future funding requirements will depend on many factors, including, but not limited to:

- the rate of progress in the development of our product candidates;
- the costs of development efforts for our product candidates, such as pamrevlumab, that are not subject to reimbursement from our collaboration partners;
- the costs necessary to obtain regulatory approvals, if any, for our product candidates in the United States ("U.S."), China and other
 jurisdictions, and the costs of post-marketing studies that could be required by regulatory authorities in jurisdictions where approval
 is obtained;
- the continuation of our existing collaborations and entry into new collaborations;
- the time and unreimbursed costs necessary to commercialize products in territories in which our product candidates are approved for sale:
- the revenues from any future sales of our products as well as revenue earned from profit share, royalties and milestones;
- · the level of reimbursement or third party payor pricing available to our products;
- the costs of establishing and maintaining manufacturing operations and obtaining third party commercial supplies of our products, if any, manufactured in accordance with regulatory requirements;
- the costs we incur in maintaining domestic and foreign operations, including operations in China;
- regulatory compliance costs;
- · the costs of our commercialization efforts for roxadustat for the treatment of anemia caused by CKD in dialysis patients in China; and
- the costs we incur in the filing, prosecution, maintenance and defense of our extensive patent portfolio and other intellectual property rights.

Additional funds may not be available when we require them, or on terms that are acceptable to us. If adequate funds are not available to us on a timely basis, we may be required to delay, limit, reduce or terminate our research and development efforts or other operations or activities that may be necessary to commercialize our product candidates.

All of our recent revenue has been earned from collaboration partners for our product candidates under development.

Substantially all of our revenues recognized in recent years have been from our collaboration partners.

We will require substantial additional capital to achieve our development and commercialization goals, which for our lead product candidate, roxadustat, is currently contemplated to be provided under our existing third party collaborations with Astellas and AstraZeneca.

If either or both of these collaborations were to be terminated, we could require significant additional capital in order to proceed with development and commercialization of our product candidates, including with respect to our expected commercialization for roxadustat for the treatment of anemia caused by CKD in dialysis patients in China, or we may require additional partnering in order to help fund such development and commercialization. If adequate funds or partners are not available to us on a timely basis or on favorable terms, we may be required to delay, limit, reduce or terminate our research and development efforts or other operations.

If we are unable to continue to progress our development efforts and achieve milestones under our collaboration agreements, our revenues may decrease and our activities may fail to lead to commercial products.

Substantially all of our revenues to date have been, and a significant portion of our future revenues are expected to be, derived from our existing collaboration agreements. Revenues from research and development collaborations depend upon continuation of the collaborations, reimbursement of development costs, the achievement of milestones and royalties and profits from our product sales, if any, derived from future products developed from our research. If we are unable to successfully advance the development of our product candidates or achieve milestones, revenues under our collaboration agreements will be substantially less than expected.

Risks Related to the Development and Commercialization of Our Product Candidates

We are substantially dependent on the success of our lead product candidate, roxadustat, and our second compound in development, pamrevlumab.

To date, we have invested a substantial portion of our efforts and financial resources in the research and development of roxadustat and pamrevlumab. While we have received approval of our NDA for roxadustat in China for CKD anemia in dialysis patients, we will need to make substantial additional investments in both the development and commercialization of roxadustat worldwide and in various indications. Our near-term prospects, including maintaining our existing collaborations with Astellas and AstraZeneca, will depend heavily on successful Phase 3 development and commercialization of roxadustat, including the commercialization of roxadustat for anemia associated with CKD in dialysis dependent patients in China, expected during the second half of 2019.

Our other lead product candidate, pamrevlumab, is currently in clinical development for IPF, pancreatic cancer and DMD. Pamrevlumab requires substantial further development and investment. We do not have a collaboration partner for support of this compound, and, while we have promising open-label safety data and potential signals of efficacy, we would need to complete larger and more extensive controlled clinical trials to validate the results to date in order to continue further development of this product candidate. In addition, although there are many potentially promising indications beyond IPF, pancreatic cancer and DMD, we are still exploring indications for which further development of, and investment for, pamrevlumab may be appropriate. Accordingly, the costs and time to complete development and related risks are currently unknown. Moreover, pamrevlumab is a monoclonal antibody, which may require experience and expertise that we may not currently possess as well as financial resources that are potentially greater than those required for our small molecule lead compound, roxadustat.

The clinical and commercial success of roxadustat and pamrevlumab will depend on a number of factors, many of which are beyond our control, and we may be unable to complete the development or commercialization of roxadustat or pamrevlumab.

The clinical and commercial success of roxadustat and pamrevlumab will depend on a number of factors, including the following:

- the timely completion of data analyses from our Phase 3 clinical trials for roxadustat, which will depend substantially upon requirements for such trials imposed by the U.S. Food and Drug Administration ("FDA") and other regulatory agencies and bodies and the continued commitment and coordinated and timely performance by our third party collaboration partners, AstraZeneca and Astellas:
- the timely initiation and completion of our Phase 2 and Phase 3 clinical trials for pamrevlumab, including in IPF, pancreatic cancer and DMD:
- · our ability to demonstrate the safety and efficacy of our product candidates to the satisfaction of the relevant regulatory authorities;
- whether we are required by the FDA or other regulatory authorities to conduct additional clinical trials, and the scope and nature of such clinical trials, prior to approval to market our products;
- the timely receipt of necessary marketing approvals from the FDA and foreign regulatory authorities, including pricing and reimbursement determinations;
- the ability to successfully commercialize our product candidates, if approved, for marketing and sale by the FDA or foreign regulatory authorities, whether alone or in collaboration with others;
- our ability and the ability of our third party manufacturing partners to manufacture quantities of our product candidates at quality levels necessary to meet regulatory requirements and at a scale sufficient to meet anticipated demand at a cost that allows us to achieve profitability;
- our success in educating health care providers and patients about the benefits, risks, administration and use of our product candidates, if approved;
- acceptance of our product candidates, if approved, as safe and effective by patients and the healthcare community;
- the success of efforts to enter into relationships with large dialysis organizations involving the administration of roxadustat to dialysis patients;
- the achievement and maintenance of compliance with all regulatory requirements applicable to our product candidates;
- the maintenance of an acceptable safety profile of our products following any approval;
- the availability, perceived advantages, relative cost, relative safety, and relative efficacy of alternative and competitive treatments;

- our ability to obtain and sustain an adequate level of pricing or reimbursement for our products by third party payors;
- our ability to enforce successfully our intellectual property rights for our product candidates and against the products of potential competitors; and
- our ability to avoid or succeed in third party patent interference or patent infringement claims.

Many of these factors are beyond our control. Accordingly, we cannot assure you that we will ever be able to achieve profitability through the sale of, or royalties from, our product candidates. If we or our collaboration partners are not successful in obtaining approval for and commercializing our product candidates, or are delayed in completing those efforts, our business and operations would be adversely affected.

If our commercialization efforts for roxadustat in China are unsuccessful, our business, financial condition and results of operations will be materially harmed.

We have invested and continue to invest a significant portion of our efforts and financial resources in the development, approval and now commercialization of roxadustat for the treatment of anemia caused by CKD in dialysis patients in China, as well as in other indications and other geographic regions. With the marketing authorization received from the National Medical Products Administration ("NMPA") of roxadustat for the treatment of anemia caused by CKD in dialysis patients in China, we plan to launch commercialization efforts in China in the third quarter of 2019 with our commercialization partner AstraZeneca.

Our success of commercialization of roxadustat in China will depend on numerous factors in China, including:

- our success in the marketing, sales, and distribution of the product along with our collaboration partner AstraZeneca;
- our success in negotiating a cost effective reimbursed price with the government in China;
- acceptance of roxadustat by state-owned and state-controlled hospitals, physicians, patients and the healthcare community;
- acceptance of pricing and placement of roxadustat on China's Medical Insurance Catalogs. Refer to "Business Government Regulation - Regulation in China";
- · successfully establishing and maintaining commercial manufacturing with third parties;
- successfully manufacturing our drug substances and drug products through our subsidiary FibroGen (China) Medical Technology Development Co., Ltd. ("FibroGen Beijing");
- · receiving market authorization for roxadustat for anemia caused by CKD in non-dialysis patients;
- our success in arranging for and passing the inspection of our clinical sites by the NMPA;
- whether AstraZeneca is able to recruit and retain adequate numbers of effective sales and marketing personnel for the sale of roxadustat;
- whether we can compete successfully as a new entrant in the treatment of anemia caused by CKD in dialysis patients in China; and
- whether we will maintain sufficient funding to cover the costs and expenses associated with creating and sustaining a capable sales and marketing organization and related commercial infrastructure.

Successful commercialization of roxadustat will require significant resources and time, and there is a risk that we may not successfully commercialize roxadustat. If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize roxadustat and generate revenues, which would deprive us from additional working capital and would materially harm our business. If we do not successfully commercialize roxadustat in China, our collaboration partners and third parties may also lose confidence in our ability to execute in commercialization efforts and become less likely to collaborate with us, and our business may be harmed.

As a Company, we have no commercialization experience, and the time and resources to develop such experience are significant. If we fail to achieve and sustain commercial success for roxadustat in China, either directly or with AstraZeneca, our business would be harmed.

Commercializing roxadustat in China with AstraZeneca will require us to establish commercialization systems, including but not limited to, medical affairs, sales, pharmacovigilance, supply-chain, and distribution capabilities to perform our portion of the collaborative efforts. These efforts will require resources and time. In particular, significant resources may be necessary to successfully market, sell and distribute roxadustat to patients with anemia caused by CKD in dialysis patients. If we, along with AstraZeneca, are not successful in setting our marketing, pricing and reimbursement strategy, facilitating adoption by hospitals in China, recruiting sales and marketing personnel or in building a sales and marketing infrastructure, we will have difficulty commercializing roxadustat, which would adversely affect our business and financial condition.

As we evolve from a company primarily involved in research and development to a company potentially involved in commercialization, we may encounter difficulties in managing our growth and expanding our operations successfully.

If we are successful in advancing roxadustat and our other product candidates through the development stage towards commercialization, we will need to expand our organization, including adding marketing and sales capabilities or continuing to contract with third parties to provide these capabilities for us. As our operations expand, we expect that we will also need to manage our existing and additional relationships with various collaborative partners, suppliers and other third parties. Future growth will impose significant added responsibilities on our organization, in particular on management. Our future financial performance and our ability to commercialize roxadustat and our other product candidates and to compete effectively will depend, in part, on our ability to manage any future growth effectively. To that end, we may not be able to manage our growth efforts effectively, and hire, train and integrate additional management, administrative and sales and marketing personnel, and our failure to accomplish any of these activities could prevent us from successfully growing our company.

Although FibroGen Beijing obtained regulatory approval for roxadustat in China in December 2018, we may be unable to obtain regulatory approval for our product candidates in other countries, or such approval may be delayed or limited, due to a number of factors, many of which are beyond our control.

The clinical trials and the manufacturing of our product candidates are and will continue to be, and the marketing of our product candidates will be, subject to extensive and rigorous review and regulation by numerous government authorities in the U.S. and in other countries where we intend to develop and, if approved, market any product candidates. Before obtaining regulatory approval for the commercial sale of any product candidate, we must demonstrate through extensive preclinical trials and clinical trials that the product candidate is safe and effective for use in each indication for which approval is sought. The regulatory review and approval process is expensive and requires substantial resources and time, and in general very few product candidates that enter development receive regulatory approval. In addition, our collaboration partners for roxadustat have final control over development decisions in their respective territories and they may make decisions with respect to development or regulatory authorities that delay or limit the potential approval of roxadustat, or increase the cost of development or commercialization. Accordingly, we may be unable to successfully develop or commercialize roxadustat or pamrevlumab or any of our other product candidates.

Even though FibroGen Beijing obtained regulatory approval for roxadustat in China, we have not obtained regulatory approval for any of our product candidates in other countries and it is possible that roxadustat and pamrevlumab will never receive regulatory approval in other countries. Other regulatory authorities may take actions or impose requirements that delay, limit or deny approval of roxadustat or pamrevlumab for many reasons, including, among others:

- our failure to adequately demonstrate to the satisfaction of regulatory authorities that roxadustat is safe and effective in treating anemia in CKD or that pamrevlumab is safe and effective in treating IPF, pancreatic cancer or DMD;
- our failure to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;
- the determination by regulatory authorities that additional clinical trials are necessary to demonstrate the safety and efficacy of
 roxadustat or pamrevlumab, or that ongoing clinical trials need to be modified in design, size, conduct or implementation;
- our product candidates may exhibit an unacceptable safety signal as they advance through clinical trials, in particular controlled Phase
 3 trials:
- the clinical research organizations ("CROs") that conduct clinical trials on our behalf may take actions outside of our control that
 materially adversely impact our clinical trials;
- we or third party contractors manufacturing our product candidates may not maintain current good manufacturing practices ("cGMP"), successfully pass inspection or meet other applicable manufacturing regulatory requirements;

- · regulatory authorities may not agree with our interpretation of the data from our preclinical trials and clinical trials;
- collaboration partners may not perform or complete their clinical programs in a timely manner, or at all; or
- principal investigators may determine that one or more serious adverse events ("SAEs"), is related or possibly related to roxadustat,
 and any such determination may adversely affect our ability to obtain regulatory approval, whether or not the determination is correct.

Any of these factors, many of which are beyond our control, could jeopardize our or our collaboration partners' abilities to obtain regulatory approval for and successfully market roxadustat. Because our business and operations in the near-term are almost entirely dependent upon roxadustat, any significant delays or impediments to regulatory approval could have a material adverse effect on our business and prospects.

In China, the NMPA required that FibroGen Beijing conduct three clinical studies as a post-approval commitment: (i) a post-approval safety study in 2,000 patients; (ii) a drug-intensive monitoring study in 1,000 patients; and (iii) a dosing optimization study in approximately 300 patients on dialysis. Furthermore, in the U.S., we also expect to be required to perform additional clinical trials in order to obtain approval or as a condition to maintaining approval due to post-marketing requirements. If the FDA requires a risk evaluation and mitigation strategy ("REMS"), for any of our product candidates if approved, the substantial cost and expense of complying with a REMS or other post-marketing requirements may limit our ability to successfully commercialize our product candidates.

Preclinical, Phase 1 and Phase 2 clinical trial results may not be indicative of the results that may be obtained in larger, controlled Phase 3 clinical trials required for approval.

Clinical development is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. Success in preclinical and early clinical trials, which are often highly variable and use small sample sizes, may not be predictive of similar results in humans or in larger, controlled clinical trials, and successful results from early or small clinical trials may not be replicated or show as favorable an outcome, even if successful.

We have conducted a limited number of Phase 2 clinical trials with pamrevlumab. We have conducted a randomized placebo-controlled study in 103 IPF patients with sub-studies in an additional 57 IPF patients comparing pamrevlumab to one of two standards of care, an open-label Phase 2 dose escalation study of pamrevlumab for IPF in 89 patients and a randomized double-blind placebo controlled study for liver fibrosis in subjects with hepatitis B, and we are currently conducting an open-label randomized, active-control, neoadjuvant Phase 2 trial in pancreatic cancer combining pamrevlumab with nab-paclitaxel plus gemcitabine in 37 patients. We cannot be sure that the results we have received to date from these trials will be substantiated in larger, well-controlled Phase 3 clinical trials, that larger trials will demonstrate the safety and efficacy of pamrevlumab for these or other indications, that further studies will provide benefits over existing approved products or that new safety issues will not be uncovered in further trials. In addition, while we believe that the limited animal and human studies conducted to date suggest that pamrevlumab has the potential to arrest or reverse fibrosis and reduce tumor mass in some patients or diseases, we cannot be sure that these results will be indicative of the effects of pamrevlumab in larger human trials. In addition, the IPF and pancreatic cancer patient populations are extremely ill and routinely experience SAEs, including death, which may be attributed to pamrevlumab in a manner that negatively impacts the safety profile of our product candidate. If the additional clinical trials that we are planning or are currently conducting for pamrevlumab do not show favorable efficacy results or result in safety concerns, or if we do not meet our clinical endpoints with statistical significance, or demonstrate an acceptable risk-benefit profile, we may be prevented from or delayed in obtaining regulatory approval for pamrevlumab in one or both of these indications.

In the past we developed an earlier generation product candidate aimed at treating anemia in CKD that resulted in a clinical hold for a safety signal seen in that product in Phase 2 clinical trials. The clinical hold applied to that product candidate and roxadustat was lifted for both product candidates after submission of the requested information to the FDA. While we have not seen similar safety concerns involving roxadustat to date, some of the safety concerns associated with the treatment of patients with anemia in CKD using erythropoiesis stimulating agents ("ESAs") did not emerge for many years until placebo-controlled studies had been conducted in large numbers of patients. And while the data monitoring committee for our U.S. and Europe Phase 3 anemia trials has consistently determined that our trials should continue without modification to the protocol, safety issues may still be discovered upon review of unblinded major adverse cardiac event ("MACE") or other data. The biochemical pathways that we believe are affected by roxadustat are implicated in a variety of biological processes and disease conditions, and it is possible that the use of roxadustat to treat larger numbers of patients will demonstrate unanticipated adverse effects, including possible drug interactions, which may negatively impact the safety profile, use and market acceptance of roxadustat. We studied the potential interaction between roxadustat and three statins (atorvastatin, rosuvastatin and simvastatin), which are used to lower levels of lipids in the blood. An adverse effect associated with increased statin plasma concentration is myopathy, which typically presents in a form of myalgia. The studies indicated the potential for increased exposure to those statins when roxadustat is taken simultaneously with those statins and suggested the need for statin dose reductions for patients receiving higher statin doses. We performed additional clinical pharmacology studies to evaluate if the effect of any such interaction could be minimized or eliminated by a modification of the dosing schedule that would separate the administration of roxadustat and the statin by up to 10 hours, however, such studies showed no minimization of effect. It is possible that the potential for interaction between roxadustat and statins could lead to label provisions for statins or roxadustat relating, for example, to dose scheduling or recommended statin dose limitations. In CKD patients, statin therapy is often initiated earlier than treatment for anemia, and risks of myopathy have been shown to decrease with increased time on drug. While we believe the prior statin treatment history of such patients at established doses may reduce the risk of adverse effects from any interaction with roxadustat and facilitate any appropriate dose adjustments, we cannot be sure that this will be the case.

Our Phase 3 trials include a MACE safety endpoint, which is a composite endpoint designed to identify major safety concerns, in particular relating to cardiovascular events such as cardiovascular death, myocardial infarction and stroke. In addition, we expect that our Phase 3 clinical trials supporting approval in Europe will be required to include MACE+ as a safety endpoint which, in addition to the MACE endpoints, also incorporates measurements of hospitalization rates due to heart failure or unstable angina. As a result, our ongoing Phase 3 clinical trials may identify unanticipated safety concerns in the patient population under study. The FDA has also informed us that the MACE endpoint will need to be evaluated separately for our Phase 3 trials in non-dialysis dependent ("NDD")-CKD patients and our Phase 3 trials in dialysis dependent ("DD")-CKD patients. The MACE endpoint will be evaluated in pooled analysis across Phase 3 studies of similar study populations and requires demonstration of non-inferiority relative to comparator, which means that the MACE event rate in roxadustat-treated patients must have less than a specified probability of exceeding the rate in the comparator trial by a specified hazard ratio. The number of patients necessary in order to permit a statistical analysis with adequate ability to detect the relative risk of MACE or MACE+ events in different arms of the trial, referred to as statistical power, depends on a number of factors, including the rate at which MACE or MACE+ events occur per patient-year in the trial, treatment duration of the patients, the required hazard ratio, and the required statistical power and confidence intervals.

In addition, we cannot be sure that the potential advantages we believe roxadustat may have for treatment of patients with anemia in CKD, as compared to the use of ESAs, will be substantiated by our larger U.S. and European Phase 3 clinical trials, or that we will be able to include a discussion of such advantages in our labeling should we obtain approval. We believe that roxadustat may have certain benefits as compared to ESAs based on the data from our Phase 2 clinical trials and China Phase 3 trials conducted to date, including safety benefits, the absence of a hypertensive effect, the potential to lower cholesterol levels and the potential to correct anemia without the use of IV iron. However, our belief that roxadustat may offer those benefits is based on a limited amount of data from our clinical trials to date, and our understanding of the likely mechanisms of action for roxadustat. Some of these benefits, such as those associated with the apparent effects on blood pressure and cholesterol, are not fully understood and, even if roxadustat receives marketing approval in additional countries beyond China, we do not expect that it will be approved for the treatment of high blood pressure or high cholesterol based on the data from our Phase 3 trials, and we may not be able to refer to any such benefits in the labeling. While the data from our Phase 2 trials suggests roxadustat may reduce low-density lipoprotein ("LDL"), and reduce the ratio of LDL to high-density lipoprotein ("HDL"), the data show it may also reduce HDL, which may be a risk to patients. In addition, causes of the safety concerns associated with the use of ESAs to achieve specified target hemoglobin levels have not been fully elucidated. While we believe that the issues giving rise to these concerns with ESAs are likely due to factors other than the hemoglobin levels achieved, we cannot be certain that roxadustat will not be associated with similar, or more severe, safety concerns.

Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials after achieving positive results in early-stage development, and we may face similar setbacks. In addition, the CKD patient population has many afflictions that may cause severe illness or death, which may be attributed to roxadustat in a manner that negatively impacts the safety profile of our product candidate. The results of our completed Phase 3 clinical trials for roxadustat demonstrated efficacy, as all primary efficacy endpoints were met with statistical significance. The analysis of adverse events for reporting of MACE is ongoing; there may be unanticipated safety concerns or adverse events that prevent from or delay obtaining marketing approval for roxadustat, and even if we obtain marketing approval, any sales of roxadustat may suffer.

We do not know whether our ongoing or planned Phase 3 clinical trials in roxadustat or Phase 2 clinical trials in pamrevlumab will need to be redesigned based on interim results, be able to achieve sufficient enrollment or be completed on schedule, if at all.

Clinical trials can be delayed or terminated for a variety of reasons, including delay or failure to:

- address any physician or patient safety concerns that arise during the course of the trial;
- obtain required regulatory or institutional review board ("IRB") approval or guidance;
- reach timely agreement on acceptable terms with prospective CROs and clinical trial sites;
- recruit, enroll and retain patients through the completion of the trial;
- maintain clinical sites in compliance with clinical trial protocols;
- initiate or add a sufficient number of clinical trial sites; and
- manufacture sufficient quantities of product candidate for use in clinical trials.

In addition, we could encounter delays if a clinical trial is suspended or terminated by us, by the relevant IRBs at the sites at which such trials are being conducted, or by the FDA or other regulatory authorities. A suspension or termination of clinical trials may result from any number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, changes in laws or regulations, or a principal investigator's determination that a serious adverse event could be related to our product candidates. Any delays in completing our clinical trials will increase the costs of the trial, delay the product candidate development and approval process and jeopardize our ability to commence marketing and generate revenues. Any of these occurrences may materially and adversely harm our business and operations and prospects.

Our product candidates may cause or have attributed to them undesirable side effects or have other properties that delay or prevent their regulatory approval or limit their commercial potential.

Undesirable side effects caused by our product candidates or that may be identified as related to our product candidates by physician investigators conducting our clinical trials or even competing products in development that utilize a similar mechanism of action or act through a similar biological disease pathway could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in the delay or denial of regulatory approval by the FDA or other regulatory authorities and potential product liability claims. Adverse events and SAEs that emerge during treatment with our product candidates or other compounds acting through similar biological pathways may be deemed to be related to our product candidate and may result in:

- our Phase 3 clinical trial development plan becoming longer and more extensive;
- regulatory authorities increasing the data and information required to approve our product candidates and imposing other requirements; and
- our collaboration partners terminating our existing agreements.

The occurrence of any or all of these events may cause the development of our product candidates to be delayed or terminated, which could materially and adversely affect our business and prospects. Refer to "Business - Our Development Program for Roxadustat" and "Business - Pamrevlumab for the Treatment of Fibrosis and Cancer" for a discussion of the adverse events and SAEs that have emerged in clinical trials of roxadustat and pamrevlumab.

Clinical trials of our product candidates may not uncover all possible adverse effects that patients may experience.

Clinical trials are conducted in representative samples of the potential patient population, which may have significant variability. Clinical trials are by design based on a limited number of subjects and of limited duration for exposure to the product used to determine whether, on a potentially statistically significant basis, the planned safety and efficacy of any product candidate can be achieved. As with the results of any statistical sampling, we cannot be sure that all side effects of our product candidates may be uncovered, and it may be the case that only with a significantly larger number of patients exposed to the product candidate for a longer duration, that a more complete safety profile is identified. Further, even larger clinical trials may not identify rare serious adverse effects or the duration of such studies may not be sufficient to identify when those events may occur. There have been other products, including ESAs, for which safety concerns have been uncovered following approval by regulatory authorities. Such safety concerns have led to labeling changes or withdrawal of ESAs products from the market. While our most advanced product candidate is chemically unique from ESAs, it or any of our product candidates may be subject to similar risks. For example, roxadustat for use in anemia in CKD is being developed to address a very diverse patient population expected to have many serious health conditions at the time of administration of roxadustat, including diabetes, high blood pressure and declining kidney function.

To date we have not seen evidence of significant safety concerns with our product candidates currently in clinical trials. Patients treated with our products, if approved, may experience adverse reactions and it is possible that the FDA or other regulatory authorities may ask for additional safety data as a condition of, or in connection with, our efforts to obtain approval of our product candidates. If safety problems occur or are identified after our product candidates reach the market, we may, or regulatory authorities may require us to amend the labeling of our products, recall our products or even withdraw approval for our products.

We may fail to enroll a sufficient number of patients in our clinical trials in a timely manner, which could delay or prevent clinical trials of our product candidates.

Identifying and qualifying patients to participate in clinical trials of our product candidates is critical to our success. The timing of our clinical trials depends on the rate at which we can recruit and enroll patients in testing our product candidates. Patients may be unwilling to participate in clinical trials of our product candidates for a variety of reasons, some of which may be beyond our control:

- severity of the disease under investigation;
- availability of alternative treatments;
- size and nature of the patient population;
- eligibility criteria for and design of the study in question;
- perceived risks and benefits of the product candidate under study;
- ongoing clinical trials of competitive agents;
- physicians' and patients' perceptions of the potential advantages of our product candidates being studied in relation to available therapies or other products under development;
- our CRO's and our trial sites' efforts to facilitate timely enrollment in clinical trials;
- patient referral practices of physicians; and
- ability to monitor patients and collect patient data adequately during and after treatment.

Patients may be unwilling to participate in our clinical trials for roxadustat due to adverse events observed in other drug treatments of anemia in CKD, and patients currently controlling their disease with existing ESAs may be reluctant to participate in a clinical trial with an investigational drug. We may not be able to successfully initiate or continue clinical trials if we cannot rapidly enroll a sufficient number of eligible patients to participate in the clinical trials required by regulatory agencies. If we have difficulty enrolling a sufficient number of patients to conduct our clinical trials as planned, we may need to delay, limit or terminate on-going or planned clinical trials, any of which could have a material and adverse effect on our business and prospects.

If we or third party manufacturers and other service providers on which we rely cannot manufacture sufficient quantities of our product candidates, or at sufficient quality, or perform other services we require, we may experience delays in development, regulatory approval, launch or commercialization.

Completion of our clinical trials and commercialization of our product candidates require access to, or development of, facilities to manufacture and manage our product candidates at sufficient yields and at commercial scale. Although we have entered into commercial supply agreements for the manufacture of some of our raw materials, we have not yet entered into commercial supply agreements with all of our third-party manufacturers. . We are continuing to negotiate and expect to enter into commercial supply agreements and other supply management agreements with third-party manufacturers, but we may not be able to enter into these agreements with satisfactory terms or on a timely manner.

We have limited experience manufacturing or managing third parties in manufacturing any of our product candidates in the volumes that are expected to be necessary to support large-scale clinical trials and sales. In addition, we have limited experience forecasting supply requirements or coordinating supply chain (including export management) for launch or commercialization, which is a complex process involving our third-party manufacturers and logistics providers, and for roxadustat, our collaboration partners. We may not be able to accurately forecast supplies for commercial launch, or do so in a timely manner and our efforts to establish these manufacturing and supply chain management capabilities may not meet our requirements as to quantities, scale-up, yield, cost, potency or quality in compliance with cGMP.

We have a limited amount of roxadustat and pamrevlumab in storage, limited capacity reserved at our third-party manufactures, and there are long lead times required to manufacture and scale-up the manufacture of additional supply, as required for both late-stage clinical trials, post-approval trials, and commercial supply. If we are unable to forecast, order or manufacture sufficient quantities of roxadustat or pamrevlumab on a timely basis, it may delay our development, launch or commercialization in some or all indications we are currently pursuing. For example, prior to agreement with regulatory authorities on the scope of our Phase 3 IPF trial design, there is uncertainty as to whether our supply plans will meet our clinical requirements in a timely manner. Any delay or interruption in the supply of our product candidates or products could have a material adverse effect on our business and operations.

Our clinical trials must be conducted with product produced under applicable cGMP regulations. Failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. We and even an experienced third party manufacturer may encounter difficulties in production, which difficulties may include:

- costs and challenges associated with scale-up and attaining sufficient manufacturing yields, in particular for biologic products such as pamrevlumab, which is a monoclonal antibody;
- supply chain issues, including coordination of multiple contractors in our supply chain and securing necessary licenses (such as export licenses);
- the timely availability and shelf life requirements of raw materials and supplies;
- quality control and assurance;
- shortages of qualified personnel and capital required to manufacture large quantities of product;
- compliance with regulatory requirements that vary in each country where a product might be sold;
- · capacity or forecasting limitations and scheduling availability in contracted facilities; and
- natural disasters, such as floods, storms, earthquakes, tsunamis, and droughts, or accidents such as fire, that affect facilities, possibly limit or postpone production, and increase costs.

Even if we are able to obtain regulatory approval of our product candidates, the label we obtain may limit the indicated uses for which our product candidates may be marketed.

With respect to roxadustat, we expect that regulatory approvals, if obtained at all, will limit the approved indicated uses for which roxadustat may be marketed, as ESAs have been subject to significant safety limitations on usage as directed by the "Black Box" warnings included in their labels. Refer to "Business - Roxadustat for the Treatment of Anemia in Chronic Kidney Disease - Limitations of the Current Standard of Care for Anemia in CKD". In addition, in the past, an approved ESA was voluntarily withdrawn due to serious safety issues discovered after approval. The safety concerns relating to ESAs may result in labeling for roxadustat containing similar warnings even if our Phase 3 clinical trials do not suggest that roxadustat has similar safety issues. Even if the label for roxadustat does not contain all of the warnings contained in the "Black Box" warning for ESAs, the label for roxadustat may contain other warnings that limit the market opportunity for roxadustat. These warnings could include warnings against exceeding specified hemoglobin targets and other warnings that derive from the lack of clarity regarding the basis for the safety issues associated with ESAs, even if our Phase 3 clinical trials do not themselves raise safety concerns.

As an organization, we have not successfully commercialized any drug product. Therefore, we may not be able to efficiently execute our development and commercialization plans.

We are currently conducting Phase 2 clinical trials for pamrevlumab and plan on initiating Phase 3 clinical trials for pamrevlumab in the future. We have initiated Phase 3 clinical trials of roxadustat. The conduct of Phase 3 clinical trials and the submission of a successful New Drug Application ("NDA") is a complicated process. As an organization, we have not completed a Phase 3 clinical trial before outside of China, where we received marketing authorization in December 2018 from the NMPA for the treatment of anemia caused by CKD in dialysis patients. We have limited experience in preparing, submitting and prosecuting regulatory filings, and have not received approval for an NDA before outside of China. Consequently, we may be unable to successfully and efficiently execute and complete necessary clinical trials in a way that leads to NDA submission and approval of roxadustat or for any other product candidate we are developing, even if our earlier stage clinical trials are successful. We may require more time and incur greater costs than our competitors and may not succeed in obtaining regulatory approvals of product candidates that we develop. Failure to commence or complete, or delays in, our planned clinical trials would prevent us from or delay us in commercializing roxadustat or any other product candidate we are developing.

In addition, in order for any Phase 3 clinical trial to support an NDA submission for approval, the FDA and foreign regulatory authorities require compliance with regulations and standards, including good clinical practices ("GCP") requirements for designing, conducting, monitoring, recording, analyzing, and reporting the results of clinical trials to ensure that the data and results from trials are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. Although we rely on third parties to conduct our clinical trials, we as the sponsor remain responsible for ensuring that each of these clinical trials is conducted in accordance with its general investigational plan and protocol under legal and regulatory requirements, including GCP. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of our CROs, trial sites, principal investigators or other third parties fail to comply with applicable GCP requirements, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or other regulatory authorities may require us to exclude the use of patient data from our clinical trials not conducted in compliance with GCP or perform additional clinical trials before approving our marketing applications. They may even reject our application for approval or refuse to accept our future applications for an extended time period. For example in China in March 2016, the State Drug Administration, now known as the NMPA issued guidance related to its clinical trial data integrity regulations. While trial sites and CROs bear liability for the accuracy and authenticity of data they are directly responsible for, the sponsor ultimately bears full responsibility for submitted clinical data and the drug application dossier. Fraudulent clinical data could result in a ban in China of a sponsor's product-related NDA applications for three years and other NDA applications for one year. We have taken extensive steps to ensure the integrity of our China clinical data. In China, the clinical site inspections confirmed our compliance with GCP regulations and supported our approval. However, we cannot assure you that upon inspection by a regulatory authority in other regions, such regulatory authority will determine that any of our clinical trials comply with GCP requirements or that our results will be deemed authentic or may be used in support of our regulatory submissions.

If we are unable to establish sales, marketing and distribution capabilities or enter into or maintain agreements with third parties to market and sell our product candidates, we may not be successful in commercializing our product candidates if and when they are approved.

We do not have a sales or marketing infrastructure and have no experience in the sales, marketing or distribution of pharmaceutical products in any country. To achieve commercial success for any product for which we obtain marketing approval, we will need to establish sales and marketing capabilities or make and maintain our existing arrangements with third parties to perform these services at a level sufficient to support our commercialization efforts.

To the extent that we would undertake sales and marketing of any of our products directly, there are risks involved with establishing our own sales, marketing and distribution capabilities. Factors that may inhibit our efforts to commercialize our products on our own include:

- our inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future products;
- our inability to effectively manage geographically dispersed sales and marketing teams;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- · unforeseen costs and expenses associated with creating an independent sales and marketing organization.

With respect to roxadustat, we are dependent on the commercialization capabilities of our collaboration partners, AstraZeneca and Astellas. If either such partner were to terminate its agreement with us, we would have to commercialize on our own or with another third party. We will have limited or little control over the commercialization efforts of such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products, if any, effectively. If they are not successful in commercializing our product candidates, our business and financial condition would suffer.

We face substantial competition, which may result in others discovering, developing or commercializing products before, or more successfully, than we do.

The development and commercialization of new pharmaceutical products is highly competitive. Our future success depends on our ability to achieve and maintain a competitive advantage with respect to the development and commercialization of our product candidates. Our objective is to discover, develop and commercialize new products with superior efficacy, convenience, tolerability, and safety. We expect that in many cases, the products that we commercialize will compete with existing, market-leading products of companies that have large, established commercial organizations.

If roxadustat is approved and launched commercially, competing drugs are expected to include ESAs, particularly in those patient segments where ESAs are used. Currently available ESAs include epoetin alfa (EPOGEN ®, marketed by Amgen Inc. in the U.S., Procrit ® and Erypo ®/Eprex ®, marketed by Johnson & Johnson Inc., and Espo ® marketed by Kyowa Hakko Kirin in Japan and China), darbepoetin (Amgen/Kyowa Hakko Kirin's Aranesp ® and NESP ®) and Mircera ® marketed by Hoffmann-La Roche ("Roche") outside of the U.S. and by Vifor Pharma ("Vifor"), a Roche licensee, in the U.S. and Puerto Rico, as well as biosimilar versions of these currently marketed ESA products. ESAs have been used in the treatment of anemia in CKD for more than 20 years, serving a significant majority of DD-CKD patients. While NDD-CKD patients who are not under the care of nephrologists, including those with diabetes and hypertension, do not typically receive ESAs and are often left untreated, some patients under nephrology care may be receiving ESA therapy. It may be difficult to encourage healthcare providers and patients to switch to roxadustat from products with which they have become familiar.

We may also face competition from potential new anemia therapies currently in clinical development, including in those patient segments not currently addressed by ESAs. Companies such as GlaxoSmithKline plc ("GSK"), Bayer Corporation ("Bayer"), Akebia Therapeutics, Inc. ("Akebia"), and Japan Tobacco, are currently developing HIF prolyl hydroxylase ("HIF-PH") inhibitors for anemia in CKD indications. Akebia is currently conducting Phase 3 studies in NDD-CKD and DD-CKD, as well as additional Phase 1 and Phase 2 studies. In Japan, Mitsubishi Tanabe Pharmaceutical Corporation, Akebia's collaboration partner, started a Phase 3 program in November 2017. GSK is conducting global Phase 3 studies in NDD-CKD and DD-CKD as well as Japan Phase 3 studies. GSK and Kyowa Hakko Kirin announced in November 2018 that the two companies signed a strategic commercialization deal in Japan for daprodustat. Bayer has completed global Phase 2 studies and announced in May 2017 its HIF-PH inhibitor is now in continued development in Japan only, and its Japan Phase 3 studies in NDD-CKD and DD-CKD are underway. Japan Tobacco is also conducting Phase 3 studies in NDD-CKD and DD-CKD and DD-CKD and performent to roxadustat.

In addition, there are other companies developing biologic therapies for the treatment of other anemia indications that we may also seek to pursue in the future, including anemia of MDS. For example, Acceleron Pharma Inc., in partnership with Celgene Corporation ("Celgene"), is in Phase 3 development of protein therapeutic candidates to treat anemia and associated complications in patients with β-thalassemia and MDS, and has received orphan drug status from the European Medicines Agency ("EMA") and FDA for these indications. Celgene announced in July 2018 that it plans to submit a marketing approval application for luspatercept in the U.S. and European Union ("EU") in the first half of 2019. There may also be new therapies for renal-related diseases that could limit the market or level of reimbursement available for roxadustat if and when it is commercialized.

In China, biosimilars of epoetin alfa are offered by Chinese pharmaceutical companies such as EPIAO marketed by 3SBio Inc. as well as more than 15 other local manufacturers. We may also face competition by HIF-PH inhibitors from other companies such as Akebia, Bayer, and GSK, which was authorized by the NMPA to conduct trials in China to support its ex-China regulatory filings. Furthermore, while it is too early to understand how the NMPA will implement its recently approved guidelines to allow multinational companies to use their ex-China clinical data in their NDAs in China, these guidelines could in theory allow competitors to accelerate their NDA applications in China. Akebia announced in December 2015 that it has entered into a development and commercialization partnership with Mitsubishi Tanabe Pharmaceutical Corporation for its HIF-PH inhibitor vadadustat in Japan, Taiwan, South Korea, India, and certain other countries in Asia, and announced in April 2017 an expansion of their U.S. collaboration with Otsuka to add markets, including China. 3SBio Inc. also announced in 2016 its plan on beginning a Phase 1 clinical trial of a HIF-PH inhibitor for the China market.

The first biosimilar ESAs, Pfizer's Retacrit® (epoetin zeta), entered the U.S. market in November 2018. Market penetration of Retacrit® (epoetin zeta) and the potential addition of other biosimilar ESAs, currently under development, may alter the competitive and pricing landscape of anemia therapy in DD-CKD patients under the end stage renal disease bundle. The patents for Amgen's epoetin alfa, EPOGEN, expired in 2004 in the EU, and the final material patents in the U.S. expired in May 2015. Several biosimilar versions of currently marketed ESAs are available for sale in the EU, China and other territories. In the U.S., a few ESA biosimilars are currently under development. Sandoz, a division of Novartis, markets Binocrit ® (epoetin alfa) in Europe and may file a biosimilar Biologics License Application ("BLA") in the U.S.

The majority of the current CKD anemia market focuses on dialysis patients, who visit dialysis centers on a regular basis, typically three-times a week, and anemia therapies are administered as part of the visit. Two of the largest operators of dialysis clinics in the U.S., DaVita Healthcare Partners Inc. ("DaVita") and Fresenius Medical Care AG & Co. KGaA ("Fresenius"), collectively provide dialysis care to approximately 70% of U.S. dialysis patients, and therefore have historically won long-term contracts including rebate terms with Amgen. In January 2017, DaVita entered into a new 6-year sourcing and supply agreement with Amgen that is effective through 2022. Fresenius' contract with Amgen expired in 2015, and Fresenius is now administering Mircera® in a significant portion of its U.S. dialysis patients since Mircera was made available by Vifor. Successful penetration of this market may require a significant agreement with Fresenius or DaVita on favorable terms and on a timely basis.

If pamrevlumab is approved and launched commercially to treat IPF, competing drugs are expected to include Roche's Esbriet® (pirfenidone) and Boehringer Ingelheim Pharma GmbH & Co. KG's Ofev® (nintedanib). Nintedanib is also in development for non-small cell lung cancer and ovarian cancer. Other potential competitive product candidates in development for IPF include Biogen-Idec's BG-00011, Galapagos NV's GLPG1690, Kadmon Holdings, Inc.'s KD025, Prometic Life Sciences Inc.'s PBI-4050, and Promedior Inc.'s PRM-151. Galapagos initiated a Phase 3 study for GLPG 1690 in December 2018.

If pamrevlumab is approved and launched commercially to treat locally advanced pancreatic cancer patients who are not candidates for surgical resection, pamrevlumab may face competition from agents seeking approval in combination with gemcitibine and nab-paclitaxel from companies such as NewLink Genetics Corporation and Halozyme Therapeutics, Inc. Gemcitabine and/or nab-paclitaxel are the current standard of care in the first-line treatment of metastatic pancreatic cancer. Celgene Corporation's Abraxane ® (nab-paclitaxel) was launched in the U.S. and Europe in 2013 and 2014, and was the first drug approved in this disease in nearly a decade.

If pamrevlumab is approved and launched commercially to treat DMD, pamrevlumab may face competition for some patients from Sarepta Therapeutics, Inc. ("Sarepta"), as well as PTC Therapeutics, Santhera Pharmaceuticals, and Catabasis Pharmaceuticals.

Sarepta is researching and developing clinical candidates for many of the specific mutations in the dystrophin gene and received accelerated approval in the U.S. for its first, drug Exondys 51® (eteplirsen) for patients who have a confirmed mutation in the DMD gene that is amenable to exon 51 skipping. This mutation represents a subset of approximately 13% of patients with DMD. Sarepta recently received a negative opinion from the EMA regarding its eteplirsen application in September 2018. In addition to etepliresen, Sarepta has two additional exon skipping programs in Phase 3 development, each of which targets approximately 8% of patients with DMD. Sarepta is also developing gene therapies for the treatment of DMD and reported positive preliminary results from a Phase 1/2a program in June 2018.

Marathon Pharmaceuticals received approval for its drug Emflaza (deflazacort) on February 9, 2017 and on March 16, 2017 announced that it had sold the commercialization rights to Emflaza to PTC Therapeutics.

PTC Therapeutics' product ataluren (Translarna TM) received conditional approval in Europe in 2014, which was renewed in November 2016 with a request for a new randomized placebo-controlled 18-month study by the Committee for Medicinal Products for Human Use of the EMA, while the FDA stated in its complete response letter in October of 2017 that the FDA is unable to approve the application in its current form. Translarna targets a different set of DMD patients from those being targeted by Sarepta's existing exon-skipping therapeutic candidate; however, it is also limited to a subset of patients who carry a specific mutation.

While pamrevlumab and some other potential competitors are intended to treat DMD patients regardless of the specific mutation, there can be no assurance that clinical trials will support broadly treating DMD patients. For example, Santhera Pharmaceuticals reported positive Phase 3 data with its drug idebenone (Raxone ®/Catena ®) in a trial measuring changes in lung function for DMD patients, however the EMA rejected the application and the FDA has asked for additional data from an ongoing trial prior to considering Raxone for approval. Santhera is currently conducting the additional Phase 3 study in the U.S. and Europe.

Catabasis Pharmaceuticals reported in April 2018 positive Phase 2 data from its clinical trial candidate edasalonexent. Edasalonexent was reported to have preserved muscle function and slowed the progression of DMD compared to rates of change in the control period prior to treatment with edasalonexent. The company started a single placebo controlled Phase 3 trial in September 2018. Catabasis expects topline data from this trial in the second quarter of 2020.

The success of any or all of these potential competitive products may negatively impact the development and potential for success of pamrevlumab. In addition, any competitive products that are on the market or in development may compete with pamrevlumab for patient recruitment and enrollment for clinical trials or may force us to change our clinical trial design, including, in order to compare pamrevlumab against another drug, which may be the new standard of care.

If FG-5200 is approved and launched in China to treat corneal blindness resulting from partial thickness corneal damage without active inflammation and infection, it is likely to compete with other products designed to treat corneal damage. For example, in April 2015, a subsidiary of China Regenerative Medicine International Limited received approval for their acellular porcine cornea stroma medical device to treat patients in China with corneal ulcers and in April 2016, Guangzhou Yourvision Biotech Co. Ltd, a subsidiary of Guanhao Biotech, received approval for their acellular porcine cornea medical device to treat patients in China with infectious keratitis that does not respond to drug treatment.

Moreover, many of our competitors have significantly greater resources than we do. Large pharmaceutical companies, in particular, have extensive experience in clinical testing, obtaining regulatory approvals, recruiting patients, manufacturing pharmaceutical products, and commercialization. In the potential anemia market for roxadustat, for example, large and established companies such as Amgen and Roche, among others, compete aggressively to maintain their market shares. In particular, the currently marketed ESA products are supported by large pharmaceutical companies that have greater experience and expertise in commercialization in the anemia market, including in securing reimbursement, government contracts and relationships with key opinion leaders; conducting testing and clinical trials; obtaining and maintaining regulatory approvals and distribution relationships to market products; and marketing approved products. These companies also have significantly greater scale research and marketing capabilities than we do and may also have products that have been approved or are in later stages of development, and have collaboration agreements in our target markets with leading dialysis companies and research institutions. These competitors have in the past successfully prevented new and competing products from entering the anemia market, and we expect that their resources will represent challenges for us and our collaboration partners, AstraZeneca and Astellas. If we and our collaboration partners are not able to compete effectively against existing and potential competitors, our business and financial condition may be materially and adversely affected.

Our future commercial success depends upon attaining significant market acceptance of our product candidates, if approved, among physicians, patients, third party payors and others in the health care community.

Even if we obtain marketing approval for roxadustat, pamrevlumab or any other product candidates that we may develop or acquire in the future in all indications and geographic regions, these product candidates may not gain market acceptance among physicians, third party payors, patients and others in the health care community. Market acceptance of any approved product, including in roxadustat for the treatment of anemia caused by CKD in dialysis patients in China, depends on a number of other factors, including:

- the clinical indications for which the product is approved and the labeling required by regulatory authorities for use with the product, including any warnings that may be required in the labeling;
- acceptance by physicians and patients of the product as a safe and effective treatment and the willingness of the target patient population to try new therapies and of physicians to prescribe new therapies;
- the cost, safety, efficacy and convenience of treatment in relation to alternative treatments;
- the restrictions on the use of our products together with other medications, if any;
- the availability of adequate coverage and reimbursement or pricing by third party payors and government authorities;
- the ability of treatment providers, such as dialysis clinics, to enter into relationships with us without violating their existing agreement;
- the effectiveness of our sales and marketing efforts.

No or limited reimbursement or insurance coverage of our approved products, if any, by third party payors may render our products less attractive to patients and healthcare providers.

Market acceptance and sales of any approved products will depend significantly on reimbursement or coverage of our products by the Chinese government or third party payors, and may be affected by existing and future healthcare reform measures or prices of related products for which the government or third party reimbursement applies. Coverage and reimbursement by the government or a third party payor may depend upon a number of factors, including the payor's determination that use of a product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- · appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

The review and publication cycle for the Chinese government to update their reimbursement lists (national or provincial) is unpredictable and is outside our control.

Obtaining coverage and reimbursement approval for a product from a government or other third party payor is a time consuming and costly process that could require us to provide supporting scientific, clinical and cost-effectiveness data for the use of our products to the payor, which we may not be able to provide. Furthermore, the reimbursement policies of third party payors may significantly change in a manner that renders our clinical data insufficient for adequate reimbursement or otherwise limits the successful marketing of our products. Even if we obtain coverage for our product candidates, third party payors may not establish adequate reimbursement amounts, which may reduce the demand for, or the price of, our products. If reimbursement is not available or is available only to limited levels, we may not be able to commercialize certain of our products.

Price controls may limit the price at which products such as roxadustat, if approved, are sold. For example, reference pricing is used by various EU member states and parallel distribution, or arbitrage between low-priced and high-priced member states, can further reduce prices. In some countries, we or our partner may be required to conduct a clinical trial or other studies that compare the cost-effectiveness of our product candidates to other available products in order to obtain or maintain reimbursement or pricing approval. Publication of discounts by third party payors or authorities may lead to further pressure on the prices or reimbursement levels within the country of publication and other countries. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unacceptable levels, we or our partner may elect not to commercialize our products in such countries, and our business and financial condition could be adversely affected.

Risks Related to Our Reliance on Third Parties

If our collaborations with Astellas or AstraZeneca were terminated, or if Astellas or AstraZeneca were to prioritize other initiatives over their collaborations with us, whether as a result of a change of control or otherwise, our ability to successfully develop and commercialize our lead product candidate, roxadustat, would suffer.

We have entered into collaboration agreements with respect to the development and commercialization of our lead product candidate, roxadustat, with Astellas and AstraZeneca. These agreements provide for reimbursement of our development costs by our collaboration partners and also provide for commercialization of roxadustat throughout the major territories of the world.

Our agreements with Astellas and AstraZeneca provide each of them with the right to terminate their respective agreements with us, upon the occurrence of negative clinical results, delays in the development and commercialization of our product candidates or adverse regulatory requirements or guidance. The termination of any of our collaboration agreements would require us to fund and perform the further development and commercialization of roxadustat in the affected territory, or pursue another collaboration, which we may be unable to do, either of which could have an adverse effect on our business and operations. In addition, each of those agreements provides our respective partners the right to terminate any of those agreements upon written notice for convenience. Moreover, if Astellas or AstraZeneca, or any successor entity, were to determine that their collaborations with us are no longer a strategic priority, or if either of them or a successor were to reduce their level of commitment to their collaborations with us, our ability to develop and commercialize roxadustat could suffer. In addition, some of our collaborations are exclusive and preclude us from entering into additional collaboration agreements with other parties in the area or field of exclusivity.

If we fail to establish and maintain strategic collaborations related to our product candidates, we will bear all of the risk and costs related to the development and commercialization of any such product candidate, and we may need to seek additional financing, hire additional employees and otherwise develop expertise at significant cost. This in turn may negatively affect the development of our other product candidates as we direct resources to our most advanced product candidates.

Conflicts with our collaboration partners could jeopardize our collaboration agreements and our ability to commercialize product candidates.

Our collaboration partners have certain rights to control decisions regarding the development and commercialization of our product candidates with respect to which they are providing funding. If we have a disagreement over strategy and activities, our plans for obtaining approval may be revised and negatively affect the anticipated timing and potential for success of our product candidates. Even if a product under a collaboration agreement is approved, we will remain substantially dependent on the commercialization strategy and efforts of our collaboration partners, and neither of our collaboration partners has experience in commercialization of a novel drug such as roxadustat in the dialysis market.

With respect to our collaboration agreements for roxadustat, there are additional complexities in that we and our collaboration partners, Astellas and AstraZeneca, must reach consensus on our Phase 3 development program. Multi-party decision-making is complex and involves significant time and effort, and there can be no assurance that the parties will cooperate or reach consensus, or that one or both of our partners will not ask to proceed independently in some or all of their respective territories or functional areas of responsibility in which the applicable collaboration partner would otherwise be obligated to cooperate with us. Any disputes or lack of cooperation with us by either Astellas or AstraZeneca may negatively impact the timing or success of our planned Phase 3 clinical studies.

We intend to conduct proprietary research programs in specific disease areas that are not covered by our collaboration agreements. Our pursuit of such opportunities could, however, result in conflicts with our collaboration partners in the event that any of our collaboration partners takes the position that our internal activities overlap with those areas that are exclusive to our collaboration agreements, and we should be precluded from such internal activities. Moreover, disagreements with our collaboration partners could develop over rights to our intellectual property. In addition, our collaboration agreements may have provisions that give rise to disputes regarding the rights and obligations of the parties. Any conflict with our collaboration partners could lead to the termination of our collaboration agreements, delay collaborative activities, reduce our ability to renew agreements or obtain future collaboration agreements or result in litigation or arbitration and would negatively impact our relationship with existing collaboration partners.

Certain of our collaboration partners could also become our competitors in the future. If our collaboration partners develop competing products, fail to obtain necessary regulatory approvals, terminate their agreements with us prematurely or fail to devote sufficient resources to the development and commercialization of our product candidates, the development and commercialization of our product candidates and products could be delayed.

We rely on third parties for the conduct of most of our preclinical and clinical trials for our product candidates, and if our third party contractors do not properly and successfully perform their obligations under our agreements with them, we may not be able to obtain or may be delayed in receiving regulatory approvals for our product candidates.

We rely heavily on university, hospital, dialysis centers and other institutions and third parties, including the principal investigators and their staff, to carry out our clinical trials in accordance with our clinical protocols and designs. We also rely on a number of third party CROs to assist in undertaking, managing, monitoring and executing our ongoing clinical trials, including those for roxadustat. We expect to continue to rely on CROs, clinical data management organizations, medical institutions and clinical investigators to conduct our development efforts in the future, including our Phase 3 development program for roxadustat. We compete with many other companies for the resources of these third parties, and large pharmaceutical companies often have significantly more extensive agreements and relationships with such third party providers, and such third party providers may prioritize the requirements of such large pharmaceutical companies over ours. The third parties on whom we rely may terminate their engagements with us at any time, which may cause delay in the development and commercialization of our product candidates. If any such third party terminates its engagement with us or fails to perform as agreed, we may be required to enter into alternative arrangements, which would result in significant cost and delay to our product development program. Moreover, our agreements with such third parties generally do not provide assurances regarding employee turnover and availability, which may cause interruptions in the research on our product candidates by such third parties.

Moreover, while our reliance on these third parties for certain development and management activities will reduce our control over these activities, it will not relieve us of our responsibilities. For example, the FDA and foreign regulatory authorities require compliance with regulations and standards, including GCP requirements for designing, conducting, monitoring, recording, analyzing and reporting the results of clinical trials to ensure that the data and results from trials are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. Although we rely on third parties to conduct our clinical trials, we, as the sponsor, remain responsible for ensuring that each of these clinical trials is conducted in accordance with its general investigational plan and protocol under legal and regulatory requirements, including GCP. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, principal investigators and trial sites.

If any of our CROs, trial sites, principal investigators or other third parties fail to comply with applicable GCP requirements, other regulations, trial protocol or other requirements under their agreements with us, the quality or accuracy of the data they obtain may be compromised or unreliable, and the trials of our product candidates may not meet regulatory requirements. If trials do not meet regulatory requirements or if these third parties need to be replaced, the development of our product candidates may be delayed, suspended or terminated, regulatory authorities may require us to exclude the use of patient data from our approval applications or perform additional clinical trials before approving our marketing applications. Regulatory authorities may even reject our application for approval or refuse to accept our future applications for an extended time period. We cannot assure you that upon inspection by a regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP requirements or that our results may be used in support of our regulatory submissions. If any of these events occur, we may not be able to obtain regulatory approval for our product candidates on a timely basis, at a reasonable cost, or at all.

We currently rely, and expect to continue to rely, on third parties to conduct many aspects of our clinical studies and product manufacturing, and these third parties may not perform satisfactorily.

We do not have any operating manufacturing facilities at this time other than our roxadustat and FG-5200 manufacturing facility in China, and our current commercial manufacturing facility plans in China are not expected to satisfy the requirements necessary to support development and commercialization outside of China. Other than in and for China specifically, we do not expect to independently manufacture our products. We currently rely, and expect to continue to rely, on third parties to scale-up, manufacture and supply roxadustat and our other product candidates outside of China. Risks arising from our reliance on third party manufacturers include:

- reduced control and additional burdens of oversight as a result of using third party manufacturers for all aspects of manufacturing activities, including regulatory compliance and quality control and assurance;
- termination of manufacturing agreements, termination fees associated with such termination, or nonrenewal of manufacturing
 agreements with third parties may negatively impact our planned development and commercialization activities;
- · the possible misappropriation of our proprietary technology, including our trade secrets and know-how; and
- disruptions to the operations of our third party manufacturers or suppliers unrelated to our product, including the merger, acquisition, or bankruptcy of a manufacturer or supplier or a catastrophic event affecting our manufacturers or suppliers.

Any of these events could lead to development delays or failure to obtain regulatory approval, or affect our ability to successfully commercialize our product candidates. Some of these events could be the basis for action by the FDA or another regulatory authority, including injunction, recall, seizure or total or partial suspension of production.

The facilities used by our contract manufacturer to manufacture our product candidates must pass inspections by the FDA and other regulatory authorities. Although, except for China, we do not control the manufacturing operations of, and expect to remain completely dependent on, our contract manufacturers for manufacture of drug substance and finished drug product, we are ultimately responsible for ensuring that our product candidates are manufactured in compliance with cGMP requirements. If our contract manufacturers cannot successfully manufacture material that conforms to our or our collaboration partners' specifications, or the regulatory requirements of the FDA or other regulatory authorities, we may not be able to secure and/or maintain regulatory approval for our product candidates and our development or commercialization plans may be delayed. In addition, we have no control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. In addition, although our longer-term agreements are expected to provide for requirements to meet our quantity and quality requirements to manufacture our products candidates for clinical studies and commercial sale, we will have minimal direct control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel and we expect to rely on our audit rights to ensure that those qualifications are maintained to meet our requirements. If our contract manufacturers' facilities do not pass inspection by regulatory authorities, or if regulatory authorities do not approve these facilities for the manufacture of our products, or withdraw any such approval in the future, we would need to identify and qualify alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our products, if approved. Moreover, any failure of our third party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us or adverse regulatory consequences, including clinical holds, warnings or untitled letters, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which would be expected to significantly and adversely affect supplies of our products to us and our collaboration partners.

Any of our third party manufacturers may terminate their engagement with us at any time and we have not yet entered into any commercial supply agreements for the manufacture of active pharmaceutical ingredients ("APIs") or drug products. With respect to roxadustat, AstraZeneca and Astellas have certain rights to assume manufacturing of roxadustat and the existence of those rights may limit our ability to enter into favorable long-term supply agreements, if at all, with other third party manufacturers. In addition, our product candidates and any products that we may develop may compete with other product candidates and products for access and prioritization to manufacture. Certain third party manufacturers may be contractually prohibited from manufacturing our product due to non-compete agreements with our competitors or a commitment to grant another party priority relative to our products. There are a limited number of third party manufacturers that operate under cGMP and that might be capable of manufacturing to meet our requirements. Due to the limited number of third party manufacturers with the contractual freedom, expertise, required regulatory approvals and facilities to manufacture our products on a commercial scale, identifying and qualifying a replacement third party manufacturer would be expensive and time-consuming and may cause delay or interruptions in the production of our product candidates or products, which in turn may delay, prevent or impair our development and commercialization efforts.

We have a letter agreement with IRIX Pharmaceuticals, Inc. ("IRIX"), a third party manufacturer that we have used in the past, pursuant to which we agreed to negotiate a single source manufacturing agreement that included a right of first negotiation for the cGMP manufacture of HIF-PH inhibitors, including roxadustat, provided that IRIX is able to match any third party bids within 5%. The exclusive right to manufacture extends for five years after approval of an NDA for those compounds, and any agreement would provide that no minimum amounts would be specified until appropriate by forecast and that we and a commercialization partner would have the rights to contract with independent third parties that exceed IRIX's internal manufacturing capabilities or in the event that we or our commercialization partner determines for reasons of continuity of supply and security that such a need exists, provided that IRIX would supply no less than 65% of the product if it is able to provide this level of supply. Subsequent to the letter agreement, we and IRIX have entered into several additional service agreements. IRIX has requested in writing that we honor the letter agreement with respect to the single source manufacturing agreement, and if we were to enter into any such exclusive manufacturing agreement, there can be no assurance that IRIX will not assert a claim for right to manufacture roxadustat or that IRIX could manufacture roxadustat successfully and in accordance with applicable regulations for a commercial product and the specifications of our collaboration partners. In 2015, Patheon Pharmaceuticals Inc., a business unit of DPx Holdings B.V. ("Patheon"), acquired IRIX, and in 2017 ThermoFisher Scientific Inc. acquired Patheon.

If any third party manufacturer terminates its engagement with us or fails to perform as agreed, we may be required to find replacement manufacturers, which would result in significant cost and delay to our development programs. Although we believe that there are several potential alternative manufacturers who could manufacture our product candidates, we may incur significant delays and added costs in identifying, qualifying and contracting with any such third party or potential second source manufacturer. In any event, with any third party manufacturer we expect to enter into technical transfer agreements and share our know-how with the third party manufacturer, which can be time-consuming and may result in delays. These delays could result in a suspension or delay of marketing roxadustat.

Certain of the components of our product candidates are acquired from single-source suppliers and have been purchased without long-term supply agreements. The loss of any of these suppliers, or their failure to supply us with supplies of sufficient quantity and quality to complete our drug substance or finished drug product of acceptable quality and an acceptable price, would materially and adversely affect our business.

We do not have an alternative supplier of certain components of our product candidates. To date, we have used purchase orders for the supply of materials that we use in our product candidates. We may be unable to enter into long-term commercial supply arrangements with our vendors, or do so on commercially reasonable terms, which could have a material adverse impact upon our business. In addition, we currently rely on our contract manufacturers to purchase from third-party suppliers some of the materials necessary to produce our product candidates. We do not have direct control over the acquisition of those materials by our contract manufacturers. Moreover, we currently do not have any agreements for the commercial production of those materials.

The logistics of our supply chain, which include shipment of materials and intermediates from countries such as China and India add additional time and risk to the manufacture of our product candidates. While we have in the past maintained sufficient inventory of materials, API, and drug product to meet our and our collaboration partners' needs for roxadustat to date, the lead time and regulatory approvals required to source from and into countries outside of the U.S. increase the risk of delay and potential shortages of supply.

Risks Related to Our Intellectual Property

If our efforts to protect our proprietary technologies are not adequate, we may not be able to compete effectively in our market.

We rely upon a combination of patents, trade secret protection and contractual arrangements to protect the intellectual property related to our technologies. We will only be able to protect our products and proprietary information and technology by preventing unauthorized use by third parties to the extent that our patents, trade secrets, and contractual position allow us to do so. Any disclosure to or misappropriation by third parties of our trade secrets or confidential information could compromise our competitive position. Moreover, we are involved in, have in the past been involved in, and may in the future be involved in legal or administrative proceedings involving our intellectual property initiated by third parties, and which proceedings can result in significant costs and commitment of management time and attention. As our product candidates continue in development, third parties may attempt to challenge the validity and enforceability of our patents and proprietary information and technologies.

We also are involved in, have in the past been involved in, and may in the future be involved in initiating legal or administrative proceedings involving the product candidates and intellectual property of our competitors. These proceedings can result in significant costs and commitment of management time and attention, and there can be no assurance that our efforts would be successful in preventing or limiting the ability of our competitors to market competing products.

Composition-of-matter patents relating to the API are generally considered to be the strongest form of intellectual property protection for pharmaceutical products, as such patents provide protection not limited to any one method of use. Method-of-use patents protect the use of a product for the specified method(s), and do not prevent a competitor from making and marketing a product that is identical to our product for an indication that is outside the scope of the patented method. We rely on a combination of these and other types of patents to protect our product candidates, and there can be no assurance that our intellectual property will create and sustain the competitive position of our product candidates.

Biotechnology and pharmaceutical product patents involve highly complex legal and scientific questions and can be uncertain. Any patent applications that we own or license may fail to result in issued patents. Even if patents do successfully issue from our applications, third parties may challenge their validity or enforceability, which may result in such patents being narrowed, invalidated, or held unenforceable. Even if our patents and patent applications are not challenged by third parties, those patents and patent applications may not prevent others from designing around our claims and may not otherwise adequately protect our product candidates. If the breadth or strength of protection provided by the patents and patent applications we hold with respect to our product candidates is threatened, competitors with significantly greater resources could threaten our ability to commercialize our product candidates. Discoveries are generally published in the scientific literature well after their actual development, and patent applications in the U.S. and other countries are typically not published until 18 months after their filing, and in some cases are never published. Therefore, we cannot be certain that we or our licensors were the first to make the inventions claimed in our owned and licensed patents or patent applications, or that we or our licensors were the first to file for patent protection covering such inventions. Subject to meeting other requirements for patentability, for U.S. patent applications filed prior to March 16, 2013, the first to invent the claimed invention is entitled to receive patent protection for that invention while, outside the U.S., the first to file a patent application encompassing the invention is entitled to patent protection for the invention. The U.S. moved to a "first to file" system under the Leahy-Smith America Invents Act ("AIA"), effective March 16, 2013. This system also includes procedures for challenging issued patents and pending patent applications, which creates additional uncertainty. We may become involved in opposition or interference proceedings challenging our patents and patent applications or the patents and patent applications of others, and the outcome of any such proceedings are highly uncertain. An unfavorable outcome in any such proceedings could reduce the scope of or invalidate our patent rights, allow third parties to commercialize our technology and compete directly with us, or result in our inability to manufacture, develop or commercialize our product candidates without infringing the patent rights of others.

In addition to the protection afforded by patents, we seek to rely on trade secret protection and confidentiality agreements to protect proprietary know-how, information, or technology that is not covered by our patents. Although our agreements require all of our employees to assign their inventions to us, and we require all of our employees, consultants, advisors and any third parties who have access to our trade secrets, proprietary know-how and other confidential information and technology to enter into appropriate confidentiality agreements, we cannot be certain that our trade secrets, proprietary know-how and other confidential information and technology will not be subject to unauthorized disclosure or that our competitors will not otherwise gain access to or independently develop substantially equivalent trade secrets, proprietary know-how and other information and technology. Furthermore, the laws of some foreign countries, in particular, China, where we have operations, do not protect proprietary rights to the same extent or in the same manner as the laws of the U.S. As a result, we may encounter significant problems in protecting and defending our intellectual property globally. If we are unable to prevent unauthorized disclosure of our intellectual property related to our product candidates and technology to third parties, we may not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business and operations.

Intellectual property disputes with third parties and competitors may be costly and time consuming, and may negatively affect our competitive position.

Our commercial success may depend on our avoiding infringement of the patents and other proprietary rights of third parties as well as on enforcing our patents and other proprietary rights against third parties. Pharmaceutical and biotechnology intellectual property disputes are characterized by complex, lengthy and expensive litigation over patents and other intellectual property rights. We may initiate or become party to or be threatened with future litigation or other proceedings regarding intellectual property rights with respect to our product candidates and competing products.

As our product candidates progress toward commercialization, we or our collaboration partners may be subject to patent infringement claims from third parties. We attempt to ensure that our product candidates do not infringe third party patents and other proprietary rights. However, the patent landscape in competitive product areas is highly complex, and there may be patents of third parties of which we are unaware that may result in claims of infringement. Accordingly, there can be no assurance that our product candidates do not infringe proprietary rights of third parties, and parties making claims against us may seek and obtain injunctive or other equitable relief, which could potentially block further efforts to develop and commercialize our product candidates including roxadustat or pamrevlumab. Any litigation involving defense against claims of infringement, regardless of the merit of such claims, would involve substantial litigation expense and would be a substantial diversion of management time.

We intend, if necessary, to vigorously enforce our intellectual property in order to protect the proprietary position of our product candidates, including roxadustat and pamrevlumab. Active efforts to enforce our patents may include litigation, administrative proceedings, or both, depending on the potential benefits that might be available from those actions and the costs associated with undertaking those efforts against third parties. We carefully review and monitor publicly available information regarding products that may be competitive with our product candidates and assert our intellectual property rights where appropriate. We previously prevailed in an administrative challenge initiated by a major biopharmaceutical company regarding our intellectual property rights, maintaining our intellectual property in all relevant scope, and will continue to protect and enforce our intellectual property rights. Moreover, third parties may continue to initiate new proceedings in the U.S. and foreign jurisdictions to challenge our patents from time to time.

We may consider administrative proceedings and other means for challenging third party patents and patent applications. An unfavorable outcome in any such challenge could require us to cease using the related technology and to attempt to license rights to it from the prevailing third party, which may not be available on commercially reasonable terms, if at all, in which case our business could be harmed.

Third parties may also challenge our patents and patent applications, through interference, reexamination, *inter partes* review, and post-grant review proceedings before the U.S. Patent and Trademark Office ("USPTO") or through comparable proceedings in other territories. For example, Akebia and others have filed oppositions against certain European patents corresponding to some of the above-listed cases. In three of these proceedings, for FibroGen European Patent Nos. 1463823, 1633333, and 2322155, the European Patent Office has handed down decisions unfavorable to FibroGen. In the fourth of these proceedings, the European Patent Office issued a decision favorable to FibroGen, maintaining FibroGen European Patent No. 2322153. These decisions are currently under appeal, and these four patents are valid and enforceable pending resolution of the appeals. The ultimate outcomes of such proceedings remain uncertain, and ultimate resolution of such may take two to four years or longer. Akebia is also pursuing invalidation actions against corresponding patents in Canada and in Japan, and invalidation actions against corresponding patents in the United Kingdom have been initiated by GSK and by Akebia. While we believe these FibroGen patents will be upheld in relevant part, we note that narrowing or even revocation of any of these patents would not affect our exclusivity for roxadustat or our freedom-to-operate with respect to use of roxadustat for the treatment of anemia.

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Furthermore, there is a risk that any public announcements concerning the status or outcomes of intellectual property litigation or administrative proceedings may adversely affect the price of our stock. If securities analysts or our investors interpret such status or outcomes as negative or otherwise creating uncertainty, our common stock price may be adversely affected.

Our reliance on third parties and agreements with collaboration partners requires us to share our trade secrets, which increases the possibility that a competitor may discover them or that our trade secrets will be misappropriated or disclosed.

Our reliance on third party contractors to develop and manufacture our product candidates is based upon agreements that limit the rights of the third parties to use or disclose our confidential information, including our trade secrets and know-how. Despite the contractual provisions, the need to share trade secrets and other confidential information increases the risk that such trade secrets and information are disclosed or used, even if unintentionally, in violation of these agreements. In the highly competitive markets in which our product candidates are expected to compete, protecting our trade secrets, including our strategies for addressing competing products, is imperative, and any unauthorized use or disclosure could impair our competitive position and may have a material adverse effect on our business and operations.

In addition, our collaboration partners are larger, more complex organizations than ours, and the risk of inadvertent disclosure of our proprietary information may be increased despite their internal procedures and contractual obligations in place with our collaboration partners. Despite our efforts to protect our trade secrets and other confidential information, a competitor's discovery of such trade secrets and information could impair our competitive position and have an adverse impact on our business.

We have an extensive worldwide patent portfolio. The cost of maintaining our patent protection is high and maintaining our patent protection requires continuous review and compliance in order to maintain worldwide patent protection. We may not be able to effectively maintain our intellectual property position throughout the major markets of the world.

The USPTO and foreign patent authorities require maintenance fees and payments as well as continued compliance with a number of procedural and documentary requirements. Noncompliance may result in abandonment or lapse of the subject patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance may result in reduced royalty payments for lack of patent coverage in a particular jurisdiction from our collaboration partners or may result in competition, either of which could have a material adverse effect on our business.

We have made, and will continue to make, certain strategic decisions in balancing costs and the potential protection afforded by the patent laws of certain countries. As a result, we may not be able to prevent third parties from practicing our inventions in all countries throughout the world, or from selling or importing products made using our inventions in and into the U.S. or other countries. Third parties may use our technologies in territories in which we have not obtained patent protection to develop their own products and, further, may infringe our patents in territories which provide inadequate enforcement mechanisms, even if we have patent protection. Such third party products may compete with our product candidates, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

The laws of some foreign countries do not protect proprietary rights to the same extent as do the laws of the U.S., and we may encounter significant problems in securing and defending our intellectual property rights outside the U.S.

Many companies have encountered significant problems in protecting and defending intellectual property rights in certain countries. The legal systems of certain countries, particularly certain developing countries such as China, do not always favor the enforcement of patents, trade secrets, and other intellectual property rights, particularly those relating to pharmaceutical and biotechnology products, which could make it difficult for us to stop infringement of our patents, misappropriation of our trade secrets, or marketing of competing products in violation of our proprietary rights. In China, our intended establishment of significant operations will depend in substantial part on our ability to effectively enforce our intellectual property rights in that country. Proceedings to enforce our intellectual property rights in foreign countries could result in substantial costs and divert our efforts and attention from other aspects of our business, and could put our patents in these territories at risk of being invalidated or interpreted narrowly, or our patent applications at risk of not being granted, and could provoke third parties to assert claims against us. We may not prevail in all legal or other proceedings that we may initiate and, if we were to prevail, the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Intellectual property rights do not address all potential threats to any competitive advantage we may have.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations, and intellectual property rights may not adequately protect our business or permit us to maintain our competitive advantage. The following examples are illustrative:

- Others may be able to make compounds that are the same as or similar to our current or future product candidates but that are not
 covered by the claims of the patents that we own or have exclusively licensed.
- We or any of our licensors or strategic partners might not have been the first to make the inventions covered by the issued patent or pending patent application that we own or have exclusively licensed.
- We or any of our licensors or strategic partners might not have been the first to file patent applications covering certain of our inventions.
- Others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights.
- The prosecution of our pending patent applications may not result in granted patents.
- Granted patents that we own or have exclusively licensed may not provide us with any competitive advantages, or may be held invalid
 or unenforceable, as a result of legal challenges by our competitors.
- Patent protection on our product candidates may expire before we are able to develop and commercialize the product, or before we are able to recover our investment in the product.
- Our competitors might conduct research and development activities in the U.S. and other countries that provide a safe harbor from
 patent infringement claims for such activities, as well as in countries in which we do not have patent rights, and may then use the
 information learned from such activities to develop competitive products for sale in markets where we intend to market our product
 candidates.

Roxadustat is considered a Class 2 substance on the 2019 World Anti-Doping Agency Prohibited List which could limit sales and increase security and distribution costs for us and our partners, particularly in China.

Roxadustat is considered a Class 2 substance on the World Anti-Doping Agency ("WADA") Prohibited List. There are enhanced security and distribution procedures we and our collaboration partners and third-party contractors will have to take to limit the risk of loss of product in the supply chain. As a result, our distribution, manufacturing and sales costs for roxadustat, as well as for our partners, will be increased which will reduce profitability. In addition there is a risk of reduced sales due to patient access to this drug. This is particularly the case in China where we will not be able to sell roxadustat in private pharmacies due to the WADA classification. While private pharmacies only represent approximately 10% of the market in China, this will negatively affect sales and therefore the profitability of roxadustat and the Company as a whole.

The existence of counterfeit pharmaceutical products in pharmaceutical markets may compromise our brand and reputation and have a material adverse effect on our business, operations and prospects.

Counterfeit products, including counterfeit pharmaceutical products, are a significant problem, particularly in China. Counterfeit pharmaceuticals are products sold or used for research under the same or similar names, or similar mechanism of action or product class, but which are sold without proper licenses or approvals. Such products may be used for indications or purposes that are not recommended or approved or for which there is no data or inadequate data with regard to safety or efficacy. Such products divert sales from genuine products, often are of lower cost, often are of lower quality (having different ingredients or formulations, for example), and have the potential to damage the reputation for quality and effectiveness of the genuine product. If counterfeit pharmaceuticals illegally sold or used for research result in adverse events or side effects to consumers, we may be associated with any negative publicity resulting from such incidents. Consumers may buy counterfeit pharmaceuticals that are in direct competition with our pharmaceuticals, which could have an adverse impact on our revenues, business and results of operations. In addition, the use of counterfeit products could be used in non-clinical or clinical studies, or could otherwise produce undesirable side effects or adverse events that may be attributed to our products as well, which could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in the delay or denial of regulatory approval by the FDA or other regulatory authorities and potential product liability claims. With respect to China, although the government has recently been increasingly active in policing counterfeit pharmaceuticals, there is not yet an effective counterfeit pharmaceutical regulation control and enforcement system in China. As a result, we may not be able to prevent third parties from selling or purporting to sell our products in China. The proliferation of counterfeit pharmaceuticals has grown in recent years and may continue to grow in the future. The existence of and any increase in the sales and production of counterfeit pharmaceuticals, or the technological capabilities of counterfeiters, could negatively impact our revenues, brand reputation, business and results of operations.

Risks Related to Government Regulation

The regulatory approval process is highly uncertain and we may not obtain regulatory approval for the commercialization of our product candidates.

The time required to obtain approval by the FDA and comparable foreign regulatory authorities is unpredictable, but typically takes many years following the commencement of preclinical studies and clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions. Except in China, We have not obtained regulatory approval for any product candidate, and it is possible that neither roxadustat nor pamrevlumab, nor any future product candidates we may discover, in-license or acquire and seek to develop in the future, will obtain regulatory approval in countries other than China.

Our product candidates could fail to receive regulatory approval from the FDA or other regulatory authorities for many reasons, including:

- disagreement over the design or implementation of our clinical trials;
- failure to demonstrate that a product candidate is safe and effective for its proposed indication;
- failure of clinical trials to meet the level of statistical significance required for approval;
- failure to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;
- disagreement over our interpretation of data from preclinical studies or clinical trials;
- disagreement over whether to accept efficacy results from clinical trial sites outside the U.S. where the standard of care is potentially different from that in the U.S.;
- the insufficiency of data collected from clinical trials of our present or future product candidates to support the submission and filing of an NDA or other submission or to obtain regulatory approval;
- disapproval of the manufacturing processes or facilities of either our manufacturing plant or third party manufacturers with whom we contract for clinical and commercial supplies; or
- changes in the approval policies or regulations that render our preclinical and clinical data insufficient for approval.

The FDA or other regulatory authorities may require more information, including additional preclinical or clinical data to support approval, which may delay or prevent approval and our commercialization plans, or we may decide to abandon the development program altogether. Even if we do obtain regulatory approval, our product candidates may be approved for fewer or more limited indications than we request, approval may be contingent on the performance of costly post-marketing clinical trials, or approval may require labeling that does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate. In addition, if our product candidates produce undesirable side effects or safety issues, the FDA may require the establishment of REMS or other regulatory authorities may require the establishment of a similar strategy, that may restrict distribution of our approved products, if any, and impose burdensome implementation requirements on us. Any of the foregoing scenarios could materially harm the commercial prospects for our product candidates.

Even if we believe our current or planned clinical trials are successful, regulatory authorities may not agree that our completed clinical trials provide adequate data on safety or efficacy. Approval by one regulatory authority does not ensure approval by any other regulatory authority. However, a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory process in others. We may not be able to file for regulatory approvals and even if we file we may not receive the necessary approvals to commercialize our product candidates in any market.

If our product candidates obtain marketing approval, we will be subject to more extensive healthcare laws, regulation and enforcement and our failure to comply with those laws could have a material adverse effect on our results of operations and financial condition.

If we obtain approval in the U.S. for any of our product candidates, the regulatory requirements applicable to our operations, in particular our sales and marketing efforts, will increase significantly with respect to our operations and the potential for civil and criminal enforcement by the federal government and the states and foreign governments will increase with respect to the conduct of our business. The laws that may affect our operations in the U.S. include:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving,
 offering or paying remuneration, directly or indirectly, to induce, or in return for, the purchase or recommendation of an item or service
 reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs;
- federal civil and criminal false claims laws and civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third party payors that are false or fraudulent;
- the Health Insurance Portability and Accountability Act of 1996 ("HIPAA"), which created new federal criminal statutes that prohibit
 executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters;
- HIPAA, as amended by Health Information Technology and Clinical Health Act, and its implementing regulations, which imposes
 certain requirements relating to the privacy, security, and transmission of individually identifiable health information;
- the federal physician sunshine requirements under the Patient Protection and Affordable Care Act ("PPACA"), which requires
 manufacturers of drugs, devices, biologics, and medical supplies to report annually to the Centers for Medicare and Medicaid Services
 ("CMS"), information related to payments and other transfers of value to physicians, other healthcare providers, and teaching
 hospitals, and ownership and investment interests held by physicians and other healthcare providers and their immediate family
 members;
- foreign and state law equivalents of each of the above federal laws, such as the U.S. Foreign Corrupt Practices Act ("FCPA"), anti-kickback and false claims laws that may apply to items or services reimbursed by any third party payor, including commercial insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the applicable compliance guidance promulgated by the federal government, or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways, thus complicating compliance efforts; and
- the Trade Agreements Act ("TAA"), which requires that drugs sold to the U.S. Government must be manufactured in the U.S. or in TAA approved and designated countries. Drugs manufactured in countries not approved under the TAA, may not be sold to the U.S. without specific regulatory approval. We have little experience with this regulation and there is a risk that drugs made from Chinesemade API may not be sold to an entity of the U.S. such as the Veterans Health Administration ("VA") due to our inability to obtain regulatory approval. While there have been recent VA policy changes that appear to allow for sale of drugs from non-TAA approved countries, this policy may change or there may be additional policies or legislation that affect our ability to sell drug to the U.S.

The scope of these laws and our lack of experience in establishing the compliance programs necessary to comply with this complex and evolving regulatory environment increases the risks that we may unknowingly violate the applicable laws and regulations. If our operations are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, the exclusion from participation in federal and state healthcare programs and imprisonment, any of which could materially adversely affect our ability to operate our business and our financial results.

The impact of recent U.S. healthcare reform, its potential partial or full repeal, and other changes in the healthcare industry and in healthcare spending is currently unknown, and may adversely affect our business model.

The commercial potential for our approved products could be affected by changes in healthcare spending and policy in the U.S. and abroad. We operate in a highly regulated industry and new laws, regulations or judicial decisions, or new interpretations of existing laws, regulations or decisions, related to healthcare availability, the method of delivery or payment for healthcare products and services could negatively impact our business, operations and financial condition.

In the U.S., the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 ("MMA") altered Medicare coverage and payments for pharmaceutical products. The legislation expanded Medicare coverage for drug purchases by the elderly and introduced a new reimbursement methodology based on average sales prices for physician-administered drugs. The MMA also provided authority for limiting the number of drugs that will be covered in any therapeutic class and as a result, we expect that there will be additional pressure to reduce costs. For example, the CMS in implementing the MMA has enacted regulations that reduced capitated payments to dialysis providers. These cost reduction initiatives and other provisions of the MMA could decrease the scope of coverage and the price that may be received for any approved dialysis products and could seriously harm our business and financial condition. While the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policies and payment limitations in setting their own reimbursement rates, and any reduction in reimbursement that results from the MMA may cause a similar reduction in payments from private payors. Similar regulations or reimbursement policies have been enacted in many international markets which could similarly impact the commercial potential for our products.

Under the Medicare Improvements for Patients and Providers Act ("MIPPA"), a basic case-mix adjusted composite, or bundled, payment system commenced in January 2011 and transitioned fully by January 2014 to a single reimbursement rate for drugs and all services furnished by renal dialysis centers for Medicare beneficiaries with end-stage renal disease. Specifically, under MIPPA the bundle now covers drugs, services, lab tests and supplies under a single treatment base rate for reimbursement by the CMS based on the average cost per treatment, including the cost of ESAs and IV iron doses, typically without adjustment for usage. It is unknown whether roxadustat, if approved in the U.S., will be included in the payment bundle. Under MIPPA, agents that have no IV equivalent in the bundle are currently expected to be excluded from the bundle until 2025. If roxadustat were included in the bundle, it may reduce the price that could be charged for roxadustat, and therefore potentially limit our profitability. Based on roxadustat's differentiated mechanism of action and therapeutic effects, and discussions with our collaboration partner, we currently believe that roxadustat might not be included in the bundle. If roxadustat is reimbursed outside of the bundle, it may potentially limit or delay market penetration of roxadustat.

More recently, the PPACA was enacted in 2010 with a goal of reducing the cost of healthcare and substantially changing the way healthcare is financed by both government and private insurers. The PPACA, among other things, increases the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extends the rebate program to individuals enrolled in Medicaid managed care organizations, establishes annual fees and taxes on manufacturers of certain branded prescription drugs, and creates a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D. In addition, other legislative changes have been proposed and adopted in the U.S. since the PPACA was enacted. On August 2, 2011, the Budget Control Act of 2011 created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least \$1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of up to 2% per fiscal year, which went into effect on April 1, 2013.

It is likely that federal and state legislatures within the U.S. and foreign governments will continue to consider changes to existing healthcare legislation. We cannot predict the reform initiatives that may be adopted in the future or whether initiatives that have been adopted will be repealed or modified. The continuing efforts of the government, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce costs of healthcare may adversely affect:

- the demand for any products that may be approved for sale;
- the price and profitability of our products;
- pricing, coverage and reimbursement applicable to our products;
- the ability to successfully position and market any approved product; and
- the taxes applicable to our pharmaceutical product revenues.

Some of the provisions of the PPACA have yet to be fully implemented, while certain provisions have been subject to judicial and Congressional challenges. In January 2017, Congress voted to adopt a budget resolution for fiscal year 2017, that while not a law, is

widely viewed as the first step toward the passage of legislation that would repeal certain aspects of the PPACA. Further, on January 20, 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the Affordable Care Act to waive, defer, grant exemptions from, or delay the implementation of any provision of the Affordable Care Act that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. Congress also could consider subsequent legislation to replace elements of the Affordable Care Act that are repealed. Given these possibilities and others we may not anticipate, the full extent to which our business, results of operations and financial condition could be adversely affected by the recent proposed legislation and the Executive Order is uncertain. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our drugs.

Furthermore, legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot be sure whether additional legislative changes will be enacted, or whether FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the regulatory approvals of our product candidates, if any, may be. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent regulatory approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements.

We may not be able to conduct, or contract others to conduct, animal testing in the future, which could harm our research and development activities.

Certain laws and regulations relating to drug development require us to test our product candidates on animals before initiating clinical trials involving humans. Animal testing activities have been the subject of controversy and adverse publicity. Animal rights groups and other organizations and individuals have attempted to stop animal testing activities by pressing for legislation and regulation in these areas and by disrupting these activities through protests and other means. To the extent the activities of these groups are successful, our research and development activities may be interrupted or delayed.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could result in significant liability for us and harm our reputation.

We are exposed to the risk of employee fraud or other misconduct, including intentional failure to:

- · comply with FDA regulations or similar regulations of comparable foreign regulatory authorities;
- provide accurate information to the FDA or comparable foreign regulatory authorities;
- comply with manufacturing standards we have established;
- comply with privacy laws protecting personal information;
- comply with federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities;
- comply with the FCPA and other anti-bribery laws;
- · report financial information or data accurately;
- or disclose unauthorized activities to us.

Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions, delays in clinical trials, or serious harm to our reputation. We have adopted a code of conduct for our directors, officers and employees, but it is not always possible to identify and deter employee misconduct. The precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could harm our business, results of operations, financial condition and cash flows, including through the imposition of significant fines or other sanctions.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could harm our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations applicable to our operations in the U.S. and foreign countries. These current or future laws and regulations may impair our research, development or manufacturing efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Risks Related to Our International Operations

We are establishing international operations and seeking approval to commercialize our product candidates outside of the U.S., in particular in China, and a number of risks associated with international operations could materially and adversely affect our business.

We expect to be subject to a number of risks related with our international operations, many of which may be beyond our control. These risks include:

- different regulatory requirements for drug approvals in foreign countries;
- different standards of care in various countries that could complicate the evaluation of our product candidates;
- different U.S. and foreign drug import and export rules;
- reduced protection for intellectual property rights in certain countries;
- · changes in tariffs, trade barriers and regulatory requirements;
- different reimbursement systems and different competitive drugs indicated to treat the indications for which our product candidates are being developed;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- · compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- compliance with the FCPA, and other anti-corruption and anti-bribery laws;
- U.S. and foreign taxes, including withholding of payroll taxes;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country;
- workforce uncertainty in countries where labor unrest is more common than in the U.S.;
- · production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad;
- a reliance on CROs, clinical trial sites, principal investigators and other third parties that may be less experienced with clinical trials or have different methods of performing such clinical trials than we are used to in the U.S.;
- · potential liability resulting from development work conducted by foreign distributors; and
- business interruptions resulting from geopolitical actions, including war and terrorism, or natural disasters.

The pharmaceutical industry in China is highly regulated and such regulations are subject to change.

The pharmaceutical industry in China is subject to comprehensive government regulation and supervision, encompassing the approval, registration, manufacturing, packaging, licensing and marketing of new drugs. Refer to "Business - Government Regulation - Regulation in China" for a discussion of the regulatory requirements that are applicable to our current and planned business activities in China. In recent years, the regulatory framework in China regarding the pharmaceutical industry has undergone significant changes, and we expect that it will continue to undergo significant changes. Any such changes or amendments may result in increased compliance costs on our business or cause delays in or prevent the successful development or commercialization of our product candidates in China. For example, the NMPA recently adopted the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines, and accordingly imposed regulatory oversight earlier in our production process for roxadustat manufactured and sold in China. The change in regulatory starting material triggered an extension of the inspection to our contract manufacturer STA, which was successfully completed in October 2018. In addition, Chinese authorities have become increasingly vigilant in enforcing laws in the pharmaceutical industry, in some cases launching industry-wide investigations, oftentimes appearing to focus on foreign companies. The costs and time necessary to respond to an investigation can be material. Any failure by us or our partners to maintain compliance with applicable laws and regulations or obtain and maintain required licenses and permits may result in the suspension or termination of our business activities in China.

We are planning on using our own manufacturing facilities in China to produce roxadustat API, roxadustat drug product, and FG-5200 corneal implants. As an organization, we have limited experience in the construction, licensure, and operation of a manufacturing plant, and accordingly we cannot assure you we will be able to meet regulatory requirements to operate our plant and to sell our products.

We have two manufacturing facilities in China, with one located in Beijing and the other in Cangzhou, Hebei. In December 2018, we received the Manufacturing License for Drug Substance and Drug Product for roxadustat and GMP certification for our Beijing facility that allows us to manufacture limited commercial quantities of roxadustat capsules. We are currently planning on manufacturing commercial-scale API at our Cangzhou facility, and expect to receive a license to produce roxadustat API at that site in the second half of 2019. However, as an organization, we have limited experience licensing and operating commercial manufacturing facilities.

We will be obligated to comply with continuing cGMP requirements and there can be no assurance that we will receive and maintain all of the appropriate licenses required to manufacture our product candidates for clinical and commercial use in China. In addition, we and our product suppliers must continually spend time, money and effort in production, record-keeping and quality assurance and appropriate controls in order to ensure that any products manufactured in our facilities meet applicable specifications and other requirements for product safety, efficacy and quality and there can be no assurance that our efforts will succeed for licensure or continue to be successful in meeting these requirements.

We would require separate approval for the manufacture of FG-5200. In addition, we may convert the existing manufacturing process of FG-5200 to a semi-automated process, which may require us to show that implants from our new manufacturing process are comparable to the implants from our existing manufacturing process. There can be no assurance that we will successfully receive licensure and maintain approval for the manufacture of FG-5200, either of which would be expected to delay or preclude our ability to develop FG-5200 in China and may materially adversely affect our business and operations and prospects in China.

Manufacturing facilities in China are subject to periodic unannounced inspections by the NMPA and other regulatory authorities. We expect to depend on these facilities for our product candidates and business operations in China. Natural disasters or other unanticipated catastrophic events, including power interruptions, water shortages, storms, fires, earthquakes, terrorist attacks, government appropriation of our facilities, and wars, could significantly impair our ability to operate our manufacturing facilities. Certain equipment, records and other materials located in these facilities would be difficult to replace or would require substantial replacement lead time that would impact our ability to successfully commercialize our product candidates in China. The occurrence of any such event could materially and adversely affect our business, financial condition, results of operations, cash flows and prospects.

In addition to manufacturing, we are responsible for pharmacovigilance, medical affairs, and management of the third party distribution logistics for roxadustat in China. We have no experience in these areas as a company, and accordingly we cannot assure you we will be able to meet regulatory requirements or operate in these capacities successfully.

We are responsible for commercial manufacturing, pharmacovigilance, medical affairs, and management of the third party distribution logistics for roxadustat commercial activities in China. While we have been increasing our staffing in these areas, as a company, we have no experience managing or operating these functions for a commercial product and there can be no guarantee that we will do so efficiently or effectively. Mistakes or delays in these areas could limit our ability to successfully commercialize roxadustat in China, could limit our eventual market penetration, sales and profitability, and could subject us to significant liability in China.

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Our decision to launch roxadustat in China prior to approval in the U.S. or Europe is largely unprecedented and could be subject to significant risk, delay and expense.

Even though our subsidiary FibroGen Beijing has received marketing authorization for roxadustat for anemia caused by CKD in dialysis patients we have not yet received approval in non-dialysis patients, and are awaiting the Chinese authorities' routine inspection of our Phase 3 non-dialysis clinical trial sites. While we currently expect these site inspections to occur in the first half of 2019, the inspections could be delayed for a number of reasons, including if regulatory authorities are otherwise occupied inspecting other matters, such as certain vaccine, plasma, or other issues that may be pressing for the country.

We also must qualify and license our Cangzhou manufacturing facility for manufacture of roxadustat API prior to launch. We expect this to occur in the third quarter of 2019, however, delays or problems obtaining such licensure would delay launch.

In addition, negative safety data from the U.S. or European Phase 3 trials could affect the NMPA approval process or label for roxadustat. Any such developments could delay or limit our commercialization plans for roxadustat in China. It is possible that other unforeseen delays in the China regulatory process could have a material adverse effect on our development and commercialization of roxadustat in China.

In addition we will be required to conduct a 2,000 subject post-approval safety study to demonstrate the long-term safety of roxadustat, as well as provide period reporting to the authorities on GMP and quality compliance at our manufacturing facilities. If safety issues arise in this study, or generally after commercialization, our commercialization plans and profitability in China could be negatively impacted.

We and our collaboration partner in China, AstraZeneca, may experience difficulties in successfully generating sales of roxadustat in China.

We and AstraZeneca have a profit sharing arrangement with respect to roxadustat in China and any difficulties we may experience in generating sales will affect our bottom line. Difficulties may be related to our ability to obtain reasonable pricing, reimbursement, hospital listing, and tendering, or other difficulties related to distribution, marketing, and sales efforts in China. Sales of roxadustat in China may be limited due to the complex nature of the healthcare system, low average personal income, pricing controls, still developing infrastructure and potentially rapid competition from other products. In particular, if we are unable to obtain reimbursement for roxadustat through the 2019 update to the NRDL, we may have to wait a substantial period of time before the reimbursement drug list is updated again. Without government reimbursement, many patients will not be able to afford roxadustat, since private commercial health insurance is rare, and our business and operations could be adversely affected. Therefore reimbursement and obtaining hospital listing is critical to roxadustat's near-term commercial success in China.

The market for treatment of anemia in CKD in China is highly competitive.

Although we have now received approval for roxadustat for the treatment of anemia caused by CKD in dialysis patients in China, and even if roxadustat receives approval for anemia caused by CKD in non-dialysis patients, it faces intense competition in the market for treatment of anemia in CKD. Roxadustat would compete with ESAs, which are offered by established multinational pharmaceutical companies such as Kyowa Hakko Kirin China Pharmaceutical Co., Ltd., Roche and Chinese pharmaceutical companies such as 3SBio Inc. and Di'ao Group Chengdu Diao Jiuhong Pharmaceutical Factory. Many of these competitors have substantially greater name recognition, scientific, financial, and marketing resources, as well as established distribution capabilities. Many of our competitors have more resources to develop or acquire, and more experience in developing or acquiring, new products and in creating market awareness for those products. Many of these competitors have significantly more experience than we have in navigating the Chinese regulatory framework regarding the development, manufacturing and marketing of drugs in China, as well as in marketing and selling anemia products in China. Additionally, we believe that most patients with anemia in CKD in China are currently being treated with traditional Chinese medicine, which is widely accepted and highly prevalent in China. Traditional Chinese medicine treatments are often oral and thus convenient and low-cost, and practitioners of traditional Chinese medicine are numerous and accessible in China. As a result, it may be difficult to persuade patients with anemia in CKD to switch from traditional Chinese medicine to roxadustat.

The Chinese government is implementing a new "Two Invoices" regulation which could affect the way we structure our distributorship relationships in China for roxadustat.

The Chinese government is implementing new regulations that impact distribution of pharmaceutical products in China. These regulations generally require that at most two invoices may be issued throughout the distribution chain. Failure to comply with the "Two-Invoices" regulations would prevent us from accessing the market in China. We are planning on modifying the distribution responsibilities under the China Agreement between AstraZeneca and FibroGen such that FibroGen would engage distributors and a third party logistics provider, and both companies will work together to manage the distribution network. FibroGen China has never managed distribution of pharmaceutical products, and this new distribution structure may impose higher costs or limit or delay our ability to sell products to our principal customers, and may limit the near term sales of our products.

There is no assurance that roxadustat will be included in the Medical Insurance Catalogs.

Eligible participants in the national basic medical insurance program in China, which consists of mostly urban residents, are entitled to reimbursement from the social medical insurance fund for up to the entire cost of medicines that are included in the Medical Insurance Catalogs. Refer to "Business - Government Regulation - Regulation in China." We believe that the inclusion of a drug in the Medical Insurance Catalogs can substantially improve the sales of a drug in China. The Ministry of Labor and Social Security in China ("MLSS") together with other government authorities, select medicines to be included in the Medical Insurance Catalogs based on a variety of factors, including treatment requirements, frequency of use, effectiveness and price. The MLSS also occasionally removes medicines from such catalogs. There can be no assurance that roxadustat will be included, and once included, remain in the Medical Insurance Catalogs. The exclusion or removal of roxadustat from the Medical Insurance Catalogs may materially and adversely affect sales of roxadustat.

Even if FG-5200 can be manufactured successfully and achieve regulatory approval, we may not achieve commercial success.

We have not yet received a license to manufacture FG-5200 in our Beijing manufacturing facility or at scale, and we will have to show that FG-5200 produced in our China manufacturing facility meets the applicable regulatory requirements. There can be no assurance that we can meet these requirements or that FG-5200 can be approved for development, manufacture and sale in China.

Even if we are able to manufacture and develop FG-5200 as a medical device in China, the size and length of any potential clinical trials required for approval are uncertain and we are unable to predict the time and investment required to obtain regulatory approval. Moreover, even if FG-5200 can be successfully developed for approval in China, our product candidate would require extensive training and investment in assisting physicians in the use of FG-5200.

The retail prices of any product candidates that we develop may be subject to control, including periodic downward adjustment, by Chinese government authorities.

The price for pharmaceutical products is highly regulated in China, both at the national and provincial level. Price controls may reduce prices to levels significantly below those that would prevail in less regulated markets, or limit the volume of products that may be sold, either of which may have a material and adverse effect on potential revenues from sales of roxadustat in China. Moreover, the process and timing for the implementation of price restrictions is unpredictable, which may cause potential revenues from the sales of roxadustat to fluctuate from period to period.

If our planned business activities in China fall within a restricted category under the China Catalog for Guidance for Foreign Investment, we will need to operate in China through a variable interest entity ("VIE") structure.

The China Catalog for Guidance for Foreign Investment sets forth the industries and sectors that the Chinese government encourages and restricts with respect to foreign investment and participation. The Catalog for Guidance for Foreign Investment is subject to revision from time to time by the China Ministry of Commerce. While we currently do not believe the development and marketing of roxadustat falls within a restricted category under the Catalog for Guidance for Foreign Investment, if roxadustat does fall under such a restricted category, we will need to operate in China through a VIE structure. A VIE structure involves a wholly foreign-owned enterprise that would control and receive the economic benefits of a domestic Chinese company through various contractual relationships. Such a structure would subject us to a number of risks that may have an adverse effect on our business, including that the Chinese government may determine that such contractual arrangements do not comply with applicable regulations, Chinese tax authorities may require us to pay additional taxes, shareholders of our VIEs may have potential conflicts of interest with us, and we may lose the ability to use and enjoy assets held by our VIEs that are important to the operations of our business if such entities go bankrupt or become subject to dissolution or liquidation proceedings. VIE structures in China have come under increasing scrutiny from accounting firms and the SEC staff. If we do attempt to use a VIE structure and are unsuccessful in structuring it so as to qualify as a VIE, we would not be able to consolidate the financial statements of the VIE with our financial statements, which could have a material adverse effect on our operating results and financial condition.

FibroGen Beijing would be subject to restrictions on paying dividends or making other payments to us, which may restrict our ability to satisfy our liquidity requirements.

We plan to conduct all of our business in China through FibroGen China Anemia Holdings, Ltd. and FibroGen Beijing. We may rely on dividends and royalties paid by FibroGen Beijing for a portion of our cash needs, including the funds necessary to service any debt we may incur and to pay our operating expenses. The payment of dividends by FibroGen Beijing is subject to limitations. Regulations in China currently permit payment of dividends only out of accumulated profits as determined in accordance with accounting standards and regulations in China. FibroGen Beijing is not permitted to distribute any profits until losses from prior fiscal years have been recouped and in any event must maintain certain minimum capital requirements. FibroGen Beijing is also required to set aside at least 10.0% of its after-tax profit based on Chinese accounting standards each year to its statutory reserve fund until the cumulative amount of such reserves reaches 50.0% of its registered capital. Statutory reserves are not distributable as cash dividends. In addition, if FibroGen Beijing incurs debt on its own behalf in the future, the agreements governing such debt may restrict its ability to pay dividends or make other distributions to us. As of December 31, 2018, approximately \$5.7 million of our cash and cash equivalents is held in China.

Any capital contributions from us to FibroGen Beijing must be approved by the Ministry of Commerce in China, and failure to obtain such approval may materially and adversely affect the liquidity position of FibroGen Beijing.

The Ministry of Commerce in China or its local counterpart must approve the amount and use of any capital contributions from us to FibroGen Beijing, and there can be no assurance that we will be able to complete the necessary government registrations and obtain the necessary government approvals on a timely basis, or at all. If we fail to do so, we may not be able to contribute additional capital to fund our Chinese operations, and the liquidity and financial position of FibroGen Beijing may be materially and adversely affected.

We may be subject to currency exchange rate fluctuations and currency exchange restrictions with respect to our operations in China, which could adversely affect our financial performance.

If roxadustat is approved for sale in China, most of our product sales will occur in local Chinese currency and our operating results will be subject to volatility from currency exchange rate fluctuations. To date, we have not hedged against the risks associated with fluctuations in exchange rates and, therefore, exchange rate fluctuations could have an adverse impact on our future operating results. Changes in value of the Renminbi against the U.S. dollar, Euro and other currencies is affected by, among other things, changes in China's political and economic conditions. Currently, the Renminbi is permitted to fluctuate within a narrow and managed band against a basket of certain foreign currencies. Any significant currency exchange rate fluctuations may have a material adverse effect on our business and financial condition.

In addition, the Chinese government imposes controls on the convertibility of the Renminbi into foreign currencies and the remittance of foreign currency out of China for certain transactions. Shortages in the availability of foreign currency may restrict the ability of FibroGen Beijing to remit sufficient foreign currency to pay dividends or other payments to us, or otherwise satisfy their foreign currency-denominated obligations. Under existing Chinese foreign exchange regulations, payments of current account items, including profit distributions, interest payments and balance of trade, can be made in foreign currencies without prior approval from the State Administration of Foreign Exchange ("SAFE") by complying with certain procedural requirements. However, approval from SAFE or its local branch is required where Renminbi is to be converted into foreign currency and remitted out of China to pay capital expenses such as the repayment of loans denominated in foreign currencies. The Chinese government may also at its discretion restrict access in the future to foreign currencies for current account transactions. If the foreign exchange control system prevents us from obtaining sufficient foreign currency to satisfy our operational requirements, our liquidity and financial position may be materially and adversely affected.

Because FibroGen Beijing's funds are held in banks that do not provide insurance, the failure of any bank in which FibroGen Beijing deposits its funds could adversely affect our business.

Banks and other financial institutions in China do not provide insurance for funds held on deposit. As a result, in the event of a bank failure, FibroGen Beijing may not have access to funds on deposit. Depending upon the amount of money FibroGen Beijing maintains in a bank that fails, its inability to have access to cash could materially impair its operations.

We may be subject to tax inefficiencies associated with our offshore corporate structure.

The tax regulations of the U.S. and other jurisdictions in which we operate are extremely complex and subject to change. New laws, new interpretations of existing laws, such as the Base Erosion Profit Shifting project initiated by the Organization for Economic Co-operation and Development and any legislation proposed by the relevant taxing authorities, or limitations on our ability to structure our operations and intercompany transactions may lead to inefficient tax treatment of our revenue, profits, royalties and distributions, if any are achieved.

In addition, we and our foreign subsidiaries have various intercompany transactions. We may not be able to obtain certain benefits under relevant tax treaties to avoid double taxation on certain transactions among our subsidiaries. If we are not able to avail ourselves of the tax treaties, we could be subject to additional taxes, which could adversely affect our financial condition and results of operations.

On December 22, 2017, the U.S. enacted the Tax Cuts and Jobs Act ("Tax Act") that instituted fundamental changes to the taxation of multinational corporations. The Tax Act includes changes to the taxation of foreign earnings by implementing a dividend exemption system, expansion of the current anti-deferral rules, a minimum tax on low-taxed foreign earnings and new measures to deter base erosion. The Tax Act also includes a permanent reduction in the corporate tax rate to 21%, repeal of the corporate alternative minimum tax, expensing of capital investment, and limitation of the deduction for interest expense. Furthermore, as part of the transition to the new tax system, a one-time transition tax is imposed on a U.S. shareholder's historical undistributed earnings of foreign affiliates. Although the Tax Act is generally effective January 1, 2018, GAAP requires recognition of the tax effects of new legislation during the reporting period that includes the enactment date, which was December 22, 2017.

As a result of the impacts of the Tax Act, the SEC provided guidance that allows us to record provisional amounts for those impacts, with the requirement that the accounting be completed in a period not to exceed one year from the date of enactment. As of December 31, 2018, we completed our analysis of the accounting for the tax effects of the Tax Act and no material adjustments were recognized as of December 31, 2018. The primary impact of the Tax Act relates to the re-measurement of deferred tax assets and liabilities resulting from the change in the corporate tax rate ("Corporate Tax Rate Change"), which was recorded as of December 2017. Developing interpretations of the provisions of the Tax Act, changes to U.S. Treasury regulations, administrative interpretations or court decisions interpreting the Tax Act in the future periods may require further adjustments to our analysis.

Our foreign operations, particularly those in China, are subject to significant risks involving the protection of intellectual property.

We seek to protect the products and technology that we consider important to our business by pursuing patent applications in China and other countries, relying on trade secrets or pharmaceutical regulatory protection or employing a combination of these methods. We note that the filing of a patent application does not mean that we will be granted a patent, or that any patent eventually granted will be as broad as requested in the patent application or will be sufficient to protect our technology. There are a number of factors that could cause our patents, if granted, to become invalid or unenforceable or that could cause our patent applications not to be granted, including known or unknown prior art, deficiencies in the patent application, or lack of originality of the technology. Furthermore, the terms of our patents are limited. The patents we hold and the patents that may be granted from our currently pending patent applications have, absent any patent term adjustment or extension, a twenty-year protection period starting from the date of application.

Intellectual property rights and confidentiality protections in China may not be as effective as those in the U.S. or other countries for many reasons, including lack of procedural rules for discovery and evidence, low damage awards, and lack of judicial independence. Implementation and enforcement of China intellectual property laws have historically been deficient and ineffective and may be hampered by corruption and local protectionism. Policing unauthorized use of proprietary technology is difficult and expensive, and we may need to resort to litigation to enforce or defend patents issued to us or to determine the enforceability and validity of our proprietary rights or those of others. The experience and capabilities of China courts in handling intellectual property litigation varies and outcomes are unpredictable. An adverse determination in any such litigation could materially impair our intellectual property rights and may harm our business.

We are subject to laws and regulations governing corruption, which will require us to develop, maintain, and implement costly compliance programs.

We must comply with a wide range of laws and regulations to prevent corruption, bribery, and other unethical business practices, including the FCPA, anti-bribery and anti-corruption laws in other countries, particularly China. The creation and implementation of international business practices compliance programs is costly and such programs are difficult to enforce, particularly where reliance on third parties is required.

Anti-bribery laws prohibit us, our employees, and some of our agents or representatives from offering or providing any personal benefit to covered government officials to influence their performance of their duties or induce them to serve interests other than the missions of the public organizations in which they serve. Certain commercial bribery rules also prohibit offering or providing any personal benefit to employees and representatives of commercial companies to influence their performance of their duties or induce them to serve interests other than their employers. The FCPA also obligates companies whose securities are listed in the U.S. to comply with certain accounting provisions requiring us to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and devise and maintain an adequate system of internal accounting controls for international operations. The anti-bribery provisions of the FCPA are enforced primarily by the Department of Justice. The SEC is involved with enforcement of the books and records provisions of the FCPA.

Compliance with these anti-bribery laws is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, the anti-bribery laws present particular challenges in the pharmaceutical industry because in many countries including China, hospitals are state-owned or operated by the government, and doctors and other hospital employees are considered foreign government officials. Furthermore, in certain countries (China in particular), hospitals and clinics are permitted to sell pharmaceuticals to their patients and are primary or significant distributors of pharmaceuticals. Certain payments to hospitals in connection with clinical studies, procurement of pharmaceuticals and other work have been deemed to be improper payments to government officials that have led to vigorous anti-bribery law enforcement actions and heavy fines in multiple jurisdictions, particularly in the U.S. and China.

It is not always possible to identify and deter violations, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations.

In the pharmaceutical industry, corrupt practices include, among others, acceptance of kickbacks, bribes or other illegal gains or benefits by the hospitals and medical practitioners from pharmaceutical manufacturers, distributors or their third party agents in connection with the prescription of certain pharmaceuticals. If our employees, affiliates, distributors or third party marketing firms violate these laws or otherwise engage in illegal practices with respect to their sales or marketing of our products or other activities involving our products, we could be required to pay damages or heavy fines by multiple jurisdictions where we operate, which could materially and adversely affect our financial condition and results of operations. The Chinese government has also sponsored anti-corruption campaigns from time to time, which could have a chilling effect on any future marketing efforts by us to new hospital customers. There have been recent occurrences in which certain hospitals have denied access to sales representatives from pharmaceutical companies because the hospitals wanted to avoid the perception of corruption. If this attitude becomes widespread among our potential customers, our ability to promote our products to hospitals may be adversely affected.

As we expand our operations in China and other jurisdictions internationally, we will need to increase the scope of our compliance programs to address the risks relating to the potential for violations of the FCPA and other anti-bribery and anti-corruption laws. Our compliance programs will need to include policies addressing not only the FCPA, but also the provisions of a variety of anti-bribery and anti-corruption laws in multiple foreign jurisdictions, including China, provisions relating to books and records that apply to us as a public company, and include effective training for our personnel throughout our organization. The creation and implementation of anti-corruption compliance programs is costly and such programs are difficult to enforce, particularly where reliance on third parties is required. Violation of the FCPA and other anti-corruption laws can result in significant administrative and criminal penalties for us and our employees, including substantial fines, suspension or debarment from government contracting, prison sentences, or even the death penalty in extremely serious cases in certain countries. The SEC also may suspend or bar us from trading securities on U.S. exchanges for violation of the FCPA's accounting provisions. Even if we are not ultimately punished by government authorities, the costs of investigation and review, distraction of our personnel, legal defense costs, and harm to our reputation could be substantial and could limit our profitability or our ability to develop or commercialize our product candidates. In addition, if any of our competitors are not subject to the FCPA, they may engage in practices that will lead to their receipt of preferential treatment from foreign hospitals and enable them to secure business from foreign hospitals in ways that are unavailable to us.

Uncertainties with respect to the China legal system could have a material adverse effect on us.

The legal system of China is a civil law system primarily based on written statutes. Unlike in a common law system, prior court decisions may be cited for reference but are not binding. Because the China legal system continues to rapidly evolve, the interpretations of many laws, regulations and rules are not always uniform and enforcement of these laws, regulations and rules involve uncertainties, which may limit legal protections available to us. Moreover, decision makers in the China judicial system have significant discretion in interpreting and implementing statutory and contractual terms, which may render it difficult for FibroGen Beijing to enforce the contracts it has entered into with our business partners, customers and suppliers. Different government departments may have different interpretations of certain laws and regulations, and licenses and permits issued or granted by one government authority may be revoked by a higher government authority at a later time. Navigating the uncertainty and change in the China legal system will require the devotion of significant resources and time, and there can be no assurance that our contractual and other rights will ultimately be enforced.

Changes in China's economic, political or social conditions or government policies could have a material adverse effect on our business and operations.

Chinese society and the Chinese economy continue to undergo significant change. Adverse changes in the political and economic policies of the Chinese government could have a material adverse effect on the overall economic growth of China, which could adversely affect our ability to conduct business in China. The Chinese government continues to adjust economic policies to promote economic growth. Some of these measures benefit the overall Chinese economy, but may also have a negative effect on us. For example, our financial condition and results of operations in China may be adversely affected by government control over capital investments or changes in tax regulations. As the Chinese pharmaceutical industry grows and evolves, the Chinese government may also implement measures to change the structure of foreign investment in this industry. We are unable to predict the frequency and scope of such policy changes, any of which could materially and adversely affect FibroGen Beijing's liquidity, access to capital and its ability to conduct business in China. Any failure on our part to comply with changing government regulations and policies could result in the loss of our ability to develop and commercialize our product candidates in China.

As part of a sweeping and ongoing government restructuring effort, China's highest legislative body, the National People's Congress, approved a plan to establish a State Administration for Market Regulation ("SAMR"), which will merge and undertake the responsibilities previously held by the State Administration for Industry and Commerce, the General Administration of Quality Supervision, Inspection and Quarantine, the Certification and Accreditation Administration, the Standardization Administration of China, and the NMPA, as well as anti-monopoly responsibilities previously held by the National Development and Reform Commission, Ministry of Commerce, and the Anti-Monopoly Office under the State Council. The restructuring also established the NMPA which has taken over much of the functions of the NMPA and will be supervised by the SAMR, while maintaining branches at the provincial level. A major government restructuring such as this one could cause significant delays and cost increases to our development, manufacturing, approval, and commercialization timelines in China. There has been turnover in government leadership and officials may be further assigned new roles and responsibilities, which may create delays and possibly new policies and priorities, and existing rules may be interpreted differently. It will take time for the restructuring to be fully implemented and the new structure to operate efficiently. As a result, our existing plans could be delayed or modified due to changes in regulations, policies or personnel decisions, all of which could have a material adverse impact on our operating results and business prospects.

Our operations in China subject us to various Chinese labor and social insurance laws, and our failure to comply with such laws may materially and adversely affect our business, financial condition and results of operations.

We are subject to China Labor Contract Law, which provides strong protections for employees and imposes many obligations on employers. The Labor Contract Law places certain restrictions on the circumstances under which employers may terminate labor contracts and require economic compensation to employees upon termination of employment, among other things. In addition, companies operating in China are generally required to contribute to labor union funds and the mandatory social insurance and housing funds. Any failure by us to comply with Chinese labor and social insurance laws may subject us to late fees, fines and penalties, or cause the suspension or termination of our ability to conduct business in China, any of which could have a material and adverse effect on business, results of operations and prospects.

Recent developments relating to the United Kingdom's referendum vote in favor of leaving the EU could adversely affect us.

The United Kingdom held a referendum on June 23, 2016 in which a majority voted for the United Kingdom's withdrawal from the EU, commonly referred to as "Brexit". As a result of this vote, negotiations are expected to commence to determine the terms of the United Kingdom's withdrawal from the EU as well as its relationship with the EU going forward, including the terms of trade between the United Kingdom and the EU. The effects of the United Kingdom's withdrawal from the EU, and the perceptions as to its impact, are expected to be far-reaching and may adversely affect business activity and economic conditions in Europe and globally and could continue to contribute to instability in global financial markets, including foreign exchange markets. The United Kingdom's withdrawal from the EU could also have the effect of disrupting the free movement of goods, services and people between the United Kingdom and the EU and could also lead to legal uncertainty and potentially divergent national laws and regulations as the United Kingdom determines which EU laws to replace or replicate, including laws that could impact our ability, or our collaborator's ability in the case of roxadustat, to obtain approval of our products or sell our products in the United Kingdom. However, the full effects of such withdrawal are uncertain and will depend on any agreements the United Kingdom may make to retain access to EU markets. Lastly, as a result of the United Kingdom's withdrawal from the EU, other European countries may seek to conduct referenda with respect to their continuing membership with the EU. Given these possibilities and others we may not anticipate, as well as the lack of comparable precedent, the full extent to which our business, results of operations and financial condition could be adversely affected by the United Kingdom's withdrawal from the EU is uncertain.

Risks Related to the Operation of Our Business

We may encounter difficulties in managing our growth and expanding our operations successfully.

As we seek to advance our product candidates through clinical trials and commercialization, we will need to expand our development, regulatory, manufacturing, commercialization and administration capabilities or contract with third parties to provide these capabilities for us. As our operations expand and we continue to undertake the efforts and expense to operate as a public reporting company, we expect that we will need to increase the responsibilities on members of management in order to manage any future growth effectively. Our failure to accomplish any of these steps could prevent us from successfully implementing our strategy and maintaining the confidence of investors in our company.

If we fail to attract and keep senior management and key personnel, in particular our chief executive officer, we may be unable to successfully develop our product candidates, conduct our clinical trials and commercialize our product candidates.

We are highly dependent on our chief executive officer, Thomas B. Neff, and other members of our senior management team. The loss of the services of Mr. Neff or any of these other individuals would be expected to significantly negatively impact the development and commercialization of our product candidates, our existing collaborative relationships and our ability to successfully implement our business strategy.

Recruiting and retaining qualified commercial, development, scientific, clinical, and manufacturing personnel are and will continue to be critical to our success, particularly as we expand our commercialization operations. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory approval of and commercialize product candidates. We may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the intense competition among numerous biopharmaceutical companies for similar personnel.

There is also significant competition, in particular in the San Francisco Bay Area, for the hiring of experienced and qualified personnel, which increases the importance of retention of our existing personnel. If we are unable to continue to attract and retain personnel with the quality and experience applicable to our product candidates, our ability to pursue our strategy will be limited and our business and operations would be adversely affected.

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If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our product candidates.

We face an inherent risk of product liability as a result of the clinical testing, manufacturing and commercialization of our product candidates. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in a product, negligence, strict liability or breach of warranty. Claims could also be asserted under state consumer protection acts. If we are unable to obtain insurance coverage at levels that are appropriate to maintain our business and operations, or if we are unable to successfully defend ourselves against product liability claims, we may incur substantial liabilities or otherwise cease operations. Product liability claims may result in:

- termination of further development of unapproved product candidates or significantly reduced demand for any approved products;
- material costs and expenses to defend the related litigation;
- a diversion of time and resources across the entire organization, including our executive management;
- product recalls, withdrawals or labeling restrictions;
- · termination of our collaboration relationships or disputes with our collaboration partners; and
- · reputational damage negatively impacting our other product candidates in development.

If we fail to obtain and retain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims, we may not be able to continue to develop our product candidates. We maintain product liability insurance in a customary amount for the stage of development of our product candidates. Although we believe that we have sufficient coverage based on the advice of our third party advisors, there can be no assurance that such levels will be sufficient for our needs. Moreover, our insurance policies have various exclusions, and we may be in a dispute with our carrier as to the extent and nature of our coverage, including whether we are covered under the applicable product liability policy. If we are not able to ensure coverage or are required to pay substantial amounts to settle or otherwise contest the claims for product liability, our business and operations would be negatively affected.

Our business and operations would suffer in the event of computer system failures.

Despite the implementation of security measures, our internal computer systems, and those of our CROs, collaboration partners, and other third parties on which we rely, are vulnerable to damage from computer viruses, unauthorized access, natural disasters, fire, terrorism, war and telecommunication and electrical failures. We upgraded our disaster and data recovery capabilities in June 2017, however, to the extent that any disruption or security breach, in particular with our partners' operations, results in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and it could result in a material disruption and delay of our drug development programs. For example, the loss of clinical trial data from completed, ongoing or planned clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data.

We depend on sophisticated information technology systems to operate our business and a cyber-attack or other breach of these systems could have a material adverse effect on our business.

We rely on information technology systems to process, transmit and store electronic information in our day-to-day operations. The size and complexity of our information technology systems makes them vulnerable to a cyber-attack, malicious intrusion, breakdown, destruction, loss of data privacy or other significant disruption. While we have recently upgraded our disaster data recovery program, a successful attack could result in the theft or destruction of intellectual property, data, or other misappropriation of assets, or otherwise compromise our confidential or proprietary information and disrupt our operations. Cyber-attacks are becoming more sophisticated and frequent. We have invested in our systems and the protection and recoverability of our data to reduce the risk of an intrusion or interruption, and we monitor and test our systems on an ongoing basis for any current or potential threats. There can be no assurance that these measures and efforts will prevent future interruptions or breakdowns. If we fail to maintain or protect our information technology systems and data integrity effectively or fail to anticipate, plan for or manage significant disruptions to these systems, we could have difficulty preventing, detecting and controlling such cyber-attacks and any such attacks could result in losses described above as well as disputes with physicians, patients and our partners, regulatory sanctions or penalties, increases in operating expenses, expenses or lost revenues or other adverse consequences, any of which could have a material adverse effect on our business, results of operations, financial condition, prospects and cash flows.

Our headquarters and data storage facilities are located near known earthquake fault zones. The occurrence of an earthquake, fire or any other catastrophic event could disrupt our operations or the operations of third parties who provide vital support functions to us, which could have a material adverse effect on our business, results of operations and financial condition.

We and some of the third party service providers on which we depend for various support functions, such as data storage, are vulnerable to damage from catastrophic events, such as power loss, natural disasters, terrorism and similar unforeseen events beyond our control. Our corporate headquarters and other facilities are located in the San Francisco Bay Area, which in the past has experienced severe earthquakes and fires.

We do not carry earthquake insurance. Earthquakes or other natural disasters could severely disrupt our operations, and have a material adverse effect on our business, results of operations, financial condition and prospects.

If a natural disaster, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters, damaged critical infrastructure, or otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place are unlikely to provide adequate protection in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which, particularly when taken together with our lack of earthquake insurance, could have a material adverse effect on our business.

Furthermore, integral parties in our supply chain are operating from single sites, increasing their vulnerability to natural disasters or other sudden, unforeseen and severe adverse events. If such an event were to affect our supply chain, it could have a material adverse effect on our business.

Risks Related to Our Common Stock

The market price of our common stock may be highly volatile, and you may not be able to resell your shares at or above your purchase price.

In general, pharmaceutical, biotechnology and other life sciences company stocks have been highly volatile in the current market. The volatility of pharmaceutical, biotechnology and other life sciences company stocks is sometimes unrelated to the operating performance of particular companies and biotechnology and life science companies stocks often respond to trends and perceptions rather than financial performance. In particular, the market price of shares of our common stock could be subject to wide fluctuations in response to the following factors:

- · results of clinical trials of our product candidates, including roxadustat and pamrevlumab;
- the timing of the release of results of and regulatory updates regarding our clinical trials;
- the level of expenses related to any of our product candidates or clinical development programs;
- results of clinical trials of our competitors' products;
- safety issues with respect to our product candidates or our competitors' products;
- · regulatory actions with respect to our product candidates and any approved products or our competitors' products;
- fluctuations in our financial condition and operating results, which will be significantly affected by the manner in which we recognize
 revenue from the achievement of milestones under our collaboration agreements;
- adverse developments concerning our collaborations and our manufacturers;
- the termination of a collaboration or the inability to establish additional collaborations;
- the publication of research reports by securities analysts about us or our competitors or our industry or negative recommendations or withdrawal of research coverage by securities analysts;
- the inability to obtain adequate product supply for any approved drug product or inability to do so at acceptable prices;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- the ineffectiveness of our internal controls;
- our failure or the failure of our competitors to meet analysts' projections or guidance that we or our competitors may give to the market;
- additions and departures of key personnel;

- announced strategic decisions by us or our competitors;
- changes in legislation or other regulatory developments affecting our product candidates or our industry;
- fluctuations in the valuation of the biotechnology industry and particular companies perceived by investors to be comparable to us;
- sales of our common stock by us, our insiders or our other stockholders;
- speculation in the press or investment community;
- announcement or expectation of additional financing efforts;
- · announcements of investigations or regulatory scrutiny of our operations or lawsuits filed against us;
- · changes in accounting principles;
- · activities of the government of China, including those related to the pharmaceutical industry as well as industrial policy generally;
- performance of other U.S. publicly traded companies with significant operations in China;
- terrorist acts, acts of war or periods of widespread civil unrest;
- · natural disasters such as earthquakes and other calamities;
- changes in market conditions for biopharmaceutical stocks;
- · changes in general market and economic conditions; and
- the other factors described in this "Risk Factors" section.

As a result of fluctuations caused by these and other factors, comparisons of our operating results across different periods may not be accurate indicators of our future performance. Any fluctuations that we report in the future may differ from the expectations of market analysts and investors, which could cause the price of our common stock to fluctuate significantly. Moreover, securities class action litigation has often been initiated against companies following periods of volatility in their stock price. This type of litigation could result in substantial costs and divert our management's attention and resources, and could also require us to make substantial payments to satisfy judgments or to settle litigation.

We have broad discretion in the use of the net proceeds from our underwritten public offerings of common stock completed on April 11, 2017 (the "April 2017 Offering") and August 24, 2017 (the "August 2017 Offering") and may not use them effectively.

The net proceeds from the April 2017 Offering is intended to be used to fund the expansion of product development in China, including developing roxadustat in additional indications beyond CKD, manufacturing and commercialization activities, as well as for general corporate purposes. The net proceeds from the August 2017 Offering is intended to be used to fund the expansion of product development, including our development of pamrevlumab beyond current Phase 2 programs, manufacturing and commercialization activities, as well as for general corporate purposes. These general corporate purposes, may include, among other things, funding research and development, clinical trials, vendor payables, potential regulatory submissions, hiring additional personnel and capital expenditures. However, we have no current commitments or obligations to use the net proceeds in the manner described above. Our management has broad discretion in the application of the balance of the net proceeds from the April 2017 Offering and the August 2017 Offering, and could spend the proceeds in ways our stockholders may not agree with or that fails to improve our business or enhance the value of our common stock. The failure by our management to use these funds effectively could result in financial losses that could harm our business, cause the price of our common stock to decline and delay the development of our product candidates

If securities or industry analysts do not continue to publish research or reports about our business, or if they change their recommendations regarding our stock adversely, our stock price and trading volume could decline.

The trading market for our common stock will be influenced by the research and reports that industry or securities analysts publish about us or our business. If one or more of the analysts who cover us downgrade our stock, our stock price would likely decline. If one or more of these analysts cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which in turn could cause our stock price or trading volume to decline.

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Our principal stockholders and management own a significant percentage of our stock and will be able to exercise significant influence over matters subject to stockholder approval.

As of January 31, 2019, our executive officers, directors and principal stockholders, together with their respective affiliates, owned approximately 39.79% of our common stock, including shares subject to outstanding options that are exercisable within 60 days after such date and shares issuable upon settlement of restricted stock units that will vest within 60 days after such date. This percentage is based upon information supplied by officers, directors and principal stockholders and Schedules 13D and 13G, if any, filed with the SEC, which information may not be accurate as of October 31, 2018. Accordingly, these stockholders will be able to exert a significant degree of influence over our management and affairs and over matters requiring stockholder approval, including the election of our board of directors and approval of significant corporate transactions. The interests of this group may differ from those of other stockholders and they may vote their shares in a way that is contrary to the way other stockholders vote their shares. This concentration of ownership could have the effect of entrenching our management and/or the board of directors, delaying or preventing a change in our control or otherwise discouraging a potential acquirer from attempting to obtain control of us, which in turn could have a material and adverse effect on the fair market value of our common stock.

Additional remedial measures that may be imposed in the proceedings instituted by the SEC against five China based accounting firms, including the Chinese affiliate of our independent registered public accounting firm, could result in our consolidated financial statements being determined to not be in compliance with the requirements of the Exchange Act.

In late 2012, the SEC commenced administrative proceedings under Rule 102(e) of its Rules of Practice and also under the Sarbanes-Oxley Act of 2002 against the Chinese affiliates of the "big four" accounting firms, including PricewaterhouseCoopers Zhong Tian CPAs Limited, the Chinese affiliate of our independent registered public accounting firm. The Rule 102(e) proceedings initiated by the SEC relate to these firms' failure to produce documents, including audit work papers, in response to the request of the SEC pursuant to Section 106 of the Sarbanes-Oxley Act of 2002, as the auditors located in China are not in a position lawfully to produce documents directly to the SEC because of restrictions under Chinese law and specific directives issued by the China Securities Regulatory Commission ("CSRC"). The issues raised by the proceedings are not specific to our auditors or to us.

In January 2014, an administrative law judge reached an initial decision that the Chinese affiliates of the "big four" accounting firms should be barred from practicing before the SEC for a period of six months. In February 2015, the Chinese affiliates of the "big four" accounting firms each agreed to a censure and to pay a fine to the SEC to settle the dispute and avoid suspension of their ability to practice before the SEC and audit U.S.-listed companies. The settlement required the firms to follow detailed procedures and to seek to provide the SEC with access to Chinese firms' audit documents via the CSRC. If future document productions fail to meet specified criteria, the SEC retains authority to impose a variety of additional remedial measures on the firms depending on the nature of the failure.

We cannot predict if the SEC will further review the four firms' compliance with specified criteria or if such further review would result in the SEC imposing additional penalties such as suspensions or commencing any further administrative proceedings. Although it does not play a substantial role (as defined under PCAOB standards) in the audit of our consolidated financial statements, if PricewaterhouseCoopers Zhong Tian CPAs Limited were denied, temporarily, the ability to practice before the SEC, our ability to produce audited consolidated financial statements for our company could be affected and we could be determined not to be in compliance with the requirements of the Exchange Act. Such a determination could ultimately lead to the delisting of our shares from the Nasdaq Global Select Market or deregistration from the SEC, or both, which would substantially reduce or effectively terminate the trading of our stock.

We may engage in future acquisitions that could disrupt our business, cause dilution to our stockholders and harm our business, results of operations, financial condition and cash flows and future prospects.

While we currently have no specific plans to acquire any other businesses, we may, in the future, make acquisitions of, or investments in, companies that we believe have products or capabilities that are a strategic or commercial fit with our present or future product candidates and business or otherwise offer opportunities for our company. In connection with these acquisitions or investments, we may:

- issue stock that would dilute our existing stockholders' percentage of ownership;
- · incur debt and assume liabilities; and
- incur amortization expenses related to intangible assets or incur large and immediate write-offs.

We may not be able to complete acquisitions on favorable terms, if at all. If we do complete an acquisition, we cannot assure you that it will ultimately strengthen our competitive position or that it will be viewed positively by customers, financial markets or investors. Furthermore, future acquisitions could pose numerous additional risks to our operations, including:

- problems integrating the purchased business, products or technologies, or employees or other assets of the acquisition target;
- increases to our expenses;
- disclosed or undisclosed liabilities of the acquired asset or company;
- diversion of management's attention from their day-to-day responsibilities;
- reprioritization of our development programs and even cessation of development and commercialization of our current product candidates;
- harm to our operating results or financial condition;
- entrance into markets in which we have limited or no prior experience; and
- potential loss of key employees, particularly those of the acquired entity.

We may not be able to complete any acquisitions or effectively integrate the operations, products or personnel gained through any such acquisition.

Provisions in our charter documents and Delaware law may have anti-takeover effects that could discourage an acquisition of us by others, even if an acquisition would be beneficial to our stockholders, and may prevent attempts by our stockholders to replace or remove our current directors or management.

Provisions in our amended and restated certificate of incorporation and amended and restated bylaws contain provisions that may have the effect of discouraging, delaying or preventing a change in control of us or changes in our management. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

- authorize "blank check" preferred stock, which could be issued by our board of directors without stockholder approval and may contain voting, liquidation, dividend and other rights superior to our common stock;
- create a classified board of directors whose members serve staggered three-year terms;
- specify that special meetings of our stockholders can be called only by our board of directors pursuant to a resolution adopted by a
 majority of the total number of directors;
- prohibit stockholder action by written consent;
- establish an advance notice procedure for stockholder approvals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our board of directors;
- provide that our directors may be removed prior to the end of their term only for cause;
- provide that vacancies on our board of directors may be filled only by a majority of directors then in office, even though less than a
 quorum;
- require a supermajority vote of the holders of our common stock or the majority vote of our board of directors to amend our bylaws;
- require a supermajority vote of the holders of our common stock to amend the classification of our board of directors into three classes and to amend certain other provisions of our certificate of incorporation.

These provisions, alone or together, could delay or prevent hostile takeovers and changes in control or changes in our management by making it more difficult for stockholders to replace members of our board of directors, which is responsible for appointing the members of our management.

Moreover, because we are incorporated in Delaware, we are governed by certain anti-takeover provisions under Delaware law which may discourage, delay or prevent someone from acquiring us or merging with us whether or not it is desired by or beneficial to our stockholders. We are subject to the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

Any provision of our amended and restated certificate of incorporation, our amended and restated bylaws or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our common stock, and could also affect the price that some investors are willing to pay for our common stock.

Changes in our tax provision or exposure to additional tax liabilities could adversely affect our earnings and financial condition.

As a multinational corporation, we are subject to income taxes in the U.S. and various foreign jurisdictions. Significant judgment is required in determining our global provision for income taxes and other tax liabilities. In the ordinary course of a global business, there are intercompany transactions and calculations where the ultimate tax determination is uncertain. Our income tax returns are subject to audits by tax authorities. Although we regularly assess the likelihood of adverse outcomes resulting from these examinations to determine our tax estimates, a final determination of tax audits or tax disputes could have an adverse effect on our results of operations and financial condition.

We are also subject to non-income taxes, such as payroll, sales, use, value-added, net worth, property, gross receipts, and goods and services taxes in the U.S., state and local, or various foreign jurisdictions. We are subject to audit and assessments by tax authorities with respect to these non-income taxes and may have exposure to additional non-income tax liabilities which could have an adverse effect on our results of operations and financial condition.

On December 22, 2017, the U.S. enacted the Tax Act that instituted fundamental changes to the taxation of multinational corporations. The Tax Act includes changes to the taxation of foreign earnings by implementing a dividend exemption system, expansion of the current anti-deferral rules, a minimum tax on low-taxed foreign earnings and new measures to deter base erosion. The Tax Act also includes a permanent reduction in the corporate tax rate to 21%, repeal of the corporate alternative minimum tax, expensing of capital investment, and limitation of the deduction for interest expense. Furthermore, as part of the transition to the new tax system, a one-time transition tax is imposed on a U.S. shareholder's historical undistributed earnings of foreign affiliates. Although the Tax Act is generally effective January 1, 2018, GAAP requires recognition of the tax effects of new legislation during the reporting period that includes the enactment date, which was December 22, 2017.

As a result of the impacts of the Tax Act, the SEC provided guidance that allows us to record provisional amounts for those impacts, with the requirement that the accounting be completed in a period not to exceed one year from the date of enactment. As of December 31, 2018, we completed our analysis of the accounting for the tax effects of the Tax Act and no material adjustments were recognized as of December 31, 2018. The primary impact of the Tax Act relates to the re-measurement of deferred tax assets and liabilities resulting from the Corporate Tax Rate Change, which was recorded as of December 31, 2017. Developing interpretations of the provisions of the Tax Act, changes to U.S. Treasury regulations, administrative interpretations or court decisions interpreting the Tax Act in the future periods may require further adjustments to our analysis.

Our amended and restated certificate of incorporation designates the state or federal courts located in the State of Delaware as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our amended and restated certificate of incorporation provides that, subject to limited exceptions, the state and federal courts located in the State of Delaware will be the sole and exclusive forum for (1) any derivative action or proceeding brought on our behalf, (2) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers or other employees to us or our stockholders, (3) any action asserting a claim against us arising pursuant to any provision of the Delaware General Corporation Law, our amended and restated certificate of incorporation or our amended and restated by-laws, or (4) any other action asserting a claim against us that is governed by the internal affairs doctrine. Any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock shall be deemed to have notice of and to have consented to the provisions of our amended and restated certificate of incorporation described above. This choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and our directors, officers and employees. Alternatively, if a court were to find these provisions of our amended and restated certificate of incorporation inapplicable to, or unenforceable in respect of, one or more of the specified types of actions or proceedings, we may incur additional costs associated with resolving such matters in other jurisdictions, which could adversely affect our business and financial condition.

Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be your sole source of gain and you may never receive a return on your investment.

You should not rely on an investment in our common stock to provide dividend income. We do not anticipate that we will pay any cash dividends to holders of our common stock in the foreseeable future and investors seeking cash dividends should not purchase our common stock. We plan to retain any earnings to invest in our product candidates and maintain and expand our operations. Therefore, capital appreciation, or an increase in your stock price, which may never occur, may be the only way to realize any return on your investment.

ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

ITEM 2. PROPERTIES

Our corporate and research and development operations are located in San Francisco, California, where we lease approximately 234,000 square feet of office and laboratory space with approximately 35,000 square feet subleased. The lease for our San Francisco headquarters expires in 2023. We also lease approximately 67,000 square feet of office and manufacturing space in Beijing, China. Our lease in China expires in 2021. We are constructing a commercial manufacturing facility of approximately 5,500 square meters in Cangzhou, China, on approximately 33,000 square meters of land. Our right to use such land expires in 2068. We believe our facilities are adequate for our current needs and that suitable additional or substitute space would be available if needed.

ITEM 3. LEGAL PROCEEEDINGS

We are not currently a party to any material legal proceedings.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

Exhibit 31.1

CERTIFICATION

- I, Thomas B. Neff., certify that;
- 1. I have reviewed this annual report on Form 10-K of FibroGen, Inc.;
- 2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
- 3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
- 4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in the Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:
- (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
- (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
- (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
- (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
- 5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
- (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
- (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 27, 2019

/s/ Thomas B. Neff

Thomas B. Neff Chairman of the Board and Chief Executive Officer (Principal Executive Officer)

Exhibit 31.2

CERTIFICATION

- I, Pat Cotroneo, certify that;
- 1. I have reviewed this annual report on Form 10-K of FibroGen, Inc.;
- 2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
- 3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
- 4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in the Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:
- (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
- (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
- (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
- (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
- 5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
- (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
- (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 27, 2019

/s/ Pat Cotroneo

Pat Cotroneo
Senior Vice President, Finance and Chief Financial
Officer (Principal Financial Officer)

Exhibit 32.1

CERTIFICATION

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), Thomas B. Neff, Chief Executive Officer of FibroGen, Inc. (the "Company"), and Pat Cotroneo, Chief Financial Officer of the Company, each hereby certifies that, to the best of his knowledge:

- 1. The Company's Annual Report on Form 10-K for the year ended December 31, 2018 (the "Annual Report"), to which this Certification is attached as Exhibit 32.1, fully complies with the requirements of Section 13(a) or Section 15(d) of the Exchange Act, and
- 2. The information contained in the Annual Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

In Witness Whereof, the undersigned have set their hands hereto as of the 27th day of February, 2019.

 /s/ Thomas B. Neff
 /s/ Pat Cotroneo

 Thomas B. Neff
 Pat Cotroneo

 Chairman of the Board and Chief Executive Officer
 Senior Vice President, Finance and Chief Financial Officer

This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of FibroGen, Inc. under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.

EXHIBIT I



Investors and Media

Press Release



Tiew printer-friendly version

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FibroGen Announces Positive Topline Results from Pooled Safety **Analyses of Roxadustat Global Phase 3 Program**

MACE/MACE+ endpoints evaluated across CKD patients not on dialysis and on dialysis Superiority in time to first MACE+ versus epoetin alfa in incident dialysis patients

SAN FRANCISCO, May 09, 2019 (GLOBE NEWSWIRE) -- FibroGen, Inc. (NASDAQ:FGEN) today announced topline results from the pooled safety analyses of the global Phase 3 program for roxadustat, an inhibitor of hypoxia-inducible-factor (HIF) prolyl hydroxylase activity (HIF-PHI). The global pivotal Phase 3 trials were conducted by FibroGen and collaboration partners AstraZeneca

and Astellas Pharma, Inc., for treatment of anemia in chronic kidney disease (CKD) patients across the non-dialysis-dependent (NDD), incident (newly initiated) dialysis, and dialysis-dependent (DD) CKD populations, enrolled from more than 50 countries.

These pooled analyses of adjudicated events for safety assessment of roxadustat are part of the overall benefit-risk assessment.

- For the planned new drug application (NDA) submission to the U.S. Food and Drug Administration (FDA), one of the key safety endpoints to be evaluated is Major Adverse Cardiac Events (MACE), a composite endpoint of all-cause mortality, stroke and myocardial infarction, in pooled analyses against placebo in NDD and against epoetin alfa in DD from the pivotal Phase 3 trials. Our NDA submission package to the FDA will be based on the totality of evidence, and we will continue to discuss the specific statistical standards with the FDA.
- For the European Medicines Agency (EMA), it was agreed that the primary safety assessment is MACE+, a composite endpoint of MACE plus heart failure requiring hospitalization and unstable angina requiring hospitalization.

"We are very pleased with what we believe are important positive results of MACE and MACE+ analyses in the dialysis-dependent, incident dialysis, and non-dialysis dependent CKD patients, supporting the safety of roxadustat in CKD patients," said Thomas B. Neff, Chief Executive Officer, FibroGen. "Combined with the positive topline efficacy in hemoglobin (Hb) control in patients with or without concomitant inflammation, reduction of transfusion, and the encouraging results from the pooled analyses of Quality of Life and estimated glomerular filtration rate (eGFR) over time, these positive safety data give us confidence as we progress in preparation for the U.S. NDA and the Marketing Authorization Application (MAA) for EMA."

Pooled MACE/MACE+ in DD-CKD Population

In the pooled analyses of around 4,000 dialysis patients, the upper bound of the 95% confidence interval (CI) was below the pre-specified non-inferiority margin for the time to first MACE+ analyses. Based on the MACE safety analyses of this population, we believe there is no clinically meaningful difference in risk of MACE between roxadustat and epoetin alfa.

Pooled MACE/MACE+ in Incident Dialysis CKD Subpopulation

The roxadustat global Phase 3 program enrolled over 1,500 incident dialysis patients, a subpopulation of DD-CKD population, which we believe offers a better setting for comparing roxadustat to epoetin alfa than the stable dialysis population, that is stable on both dialysis and erythropoiesis stimulating agent (ESA). Roxadustat demonstrated superiority to epoetin alfa in the time to first MACE+ in this subpopulation. In the MACE analysis, there is a trend toward reduced risk for patients on roxadustat, compared to epoetin alfa.

Pooled MACE/MACE+ in NDD-CKD Population

In the non-dialysis pool of approximately 4,300 patients, non-inferiority was demonstrated for roxadustat compared to placebo in the time to first MACE+, based on the upper bound of the 95% CI being below the prespecified non-inferiority margin. Based on the MACE safety analyses of this population, we believe there is no clinically meaningful difference in risk of MACE between roxadustat and placebo.

Of note, multiple MACE and MACE+ analyses in NDD-CKD from the roxadustat global Phase 3 program are being performed in intent-to-treat (ITT) analyses that demonstrated comparability of roxadustat to placebo. ITT is among the several statistical methods that we will discuss with the FDA. In these analyses, roxadustat was comparable based on a commonly applied non-inferiority margin of 1.3.

"Patients going through initiation of dialysis experience increased risks including mortality, and the NDD-CKD patients are often left untreated for anemia due to the safety concerns of the currently available therapies. We are particularly excited about the results indicating a reduction of risk of MACE+ events in incident dialysis patients, and the additional potential clinical benefits of roxadustat beyond anemia correction, to include attenuation of renal function decline and improvement of quality of life in NDD-CKD patients," said K. Peony Yu, MD, Chief Medical Officer, FibroGen. "As we accumulate a body of evidence of roxadustat efficacy and safety with these adjudicated pooled analyses, we look forward to begin discussions with U.S. FDA on NDA submission."

Further analyses of overall safety is ongoing and will inform on the overall benefit risk.

Slower eGFR Decline Observed in NDD patients

In the pooled analysis of eGFR change over time from the three NDD studies, we observed a slower eGFR decline in the roxadustat-treated patients versus placebo-treated patients in patients with baseline eGFR ≥ 15 mL/min/1.73 m², with a treatment difference of 1.62 mL/min/1.73 m² in eGFR change at 12 months from the baseline (p<0.0001), or a reduction by 38% in eGFR decline in the roxadustat arm relative to the placebo arm.

Improvements in Quality of Life Measures in NDD patients

In the pooled analysis from the three NDD studies, we observed statistically significant improvements from baseline to Week 12 in quality of life endpoints, including SF-36 Vitality subscale (p=0.0002), SF-36 Physical Functioning subscale (p=0.0369), FACT-AN Anemia subscale (p=0.0012), FACT-AN Total score (p=0.0056), and EQ-5D-SL VAS score (p=0.0005) when comparing roxadustat to placebo in CKD patients not on dialysis.

Efficacy Regardless of Inflammation Status

Roxadustat has demonstrated efficacy regardless of inflammation status as the mean achieved Hb levels and roxadustat dose requirements were not impacted by baseline c-reactive protein (CRP) levels in multiple Phase 3 studies, including in the U.S.-based SIERRAS study, which we believe is reflective of US dialysis practice under current ESA labeling restrictions. In SIERRAS, roxadustat dose requirements remained stable over time, while epoetin alfa dose requirements increased by 57% over 52 weeks in the epoetin alfa arm.

FibroGen and AstraZeneca will begin discussions with the U.S. FDA to prepare for regulatory submission, which is anticipated in September or October of 2019. We will also support Astellas' submission of MAA to the EMA thereafter.

About Anemia Associated with CKD

Anemia can be a serious medical condition in which patients have insufficient red blood cells and low levels of Hb, a protein in red blood cells that carries oxygen to cells throughout the body. Anemia in CKD is associated with increased risk of hospitalization, cardiovascular complications and death, also frequently causing significant fatigue, cognitive dysfunction and reduced quality of life. Severe anemia is common in patients with CKD, cancer, myelodysplastic syndromes (MDS), inflammatory diseases, and other serious illnesses.

Anemia is particularly prevalent in patients with CKD. The prevalence of CKD in the adult population is estimated at 10-12% globally, and is generally a progressive disease characterized by gradual loss of kidney function that may eventually lead to kidney failure, or end stage renal disease, requiring dialysis or kidney transplant to survive. Blood transfusion is used for treating life-threatening severe anemia. However, blood transfusions reduce the patient's opportunity for kidney transplant, increase risk of infections and the risk of complications such as heart failure and allergic reactions.

According to the United States Renal Data System (USRDS), over 14% of the U.S. adult population is affected by CKD, and a majority of dialysis-eligible CKD patients are currently on dialysis. It is estimated that approximately 507,000 patients are receiving dialysis in the U.S. as of 2016.

About Roxadustat

Roxadustat (FG-4592), discovered by FibroGen, is a first-in-class, orally administered small molecule currently approved in China for the treatment of anemia in CKD patients on dialysis. Roxadustat is a HIF-PHI that promotes erythropoiesis through increasing endogenous production of erythropoietin, improving iron regulation, and overcoming the negative impact of inflammation on hemoglobin syntheses and red blood cell production by downregulating hepcidin. Administration of roxadustat has been shown to induce coordinated erythropoiesis, increasing red blood cell count while maintaining plasma erythropoietin levels within or near normal physiologic range in multiple subpopulations of CKD patients, including in the presence of inflammation and without a need for supplemental intravenous iron.

FibroGen and collaboration partners are pursuing four approval pathways in major jurisdictions to prepare for commercialization worldwide:

- Astellas and FibroGen are collaborating on the development and commercialization of roxadustat for the treatment of anemia in territories including Japan, Europe, the Commonwealth of Independent States, the Middle East, and South Africa.
- AstraZeneca and FibroGen are collaborating on the development and commercialization of roxadustat for the treatment of anemia in the U.S., China, and other markets in the Americas and in Australia/New Zealand as well as Southeast Asia.

FibroGen and its partners have completed 35 Phase 1 and Phase 2 studies. The Phase 2 clinical studies have consistently demonstrated anemia correction and maintenance of hemoglobin levels in multiple subpopulations across a wide spectrum of CKD patients.

Globally, the Phase 3 program encompasses a total of 15 Phase 3 studies of roxadustat in both nondialysis-dependent and dialysis-dependent CKD patients to support independent regulatory approvals in the U.S., Europe, Japan, and China. To date, positive topline results have been announced for 12 of the Phase 3 studies, with two supporting the China NDA for treatment of anemia in CKD patients on dialysis and not on dialysis, four supporting the Japan NDA for treatment of anemia in CKD patients on dialysis, and six supporting the U.S./EU submissions including today's announcement of 3 studies by FibroGen. Roxadustat was approved by China National Medical Products Administration (NMPA) in December 2018, for treatment of anemia in CKD patients on dialysis. The Japan NDA submitted by Astellas is under review by the Japan Pharmaceuticals and Medical Devices Agency (PMDA).

Roxadustat is currently in Phase 3 clinical development for the treatment of anemia associated with MDS in the U.S. and in Phase 2/3 development for MDS in China.

About FibroGen

FibroGen, Inc., headquartered in San Francisco, California, with subsidiary offices in Beijing and Shanghai, People's Republic of China, is a leading biopharmaceutical company discovering and developing a pipeline of first-in-class therapeutics. The company applies its pioneering expertise in hypoxia-inducible factor (HIF), connective tissue growth factor (CTGF) biology, and clinical development to advance innovative medicines for the treatment of anemia, fibrotic disease, and cancer. Roxadustat, the company's most advanced product candidate, is an oral small molecule inhibitor of HIF prolyl hydroxylase activity, completing worldwide Phase 3 clinical development for the treatment of anemia in chronic kidney disease (CKD), with a New Drug Application (NDA) now approved by the National Medical Products Administration (NMPA) in China. Our partner Astellas submitted a NDA for the treatment of anemia in CKD patients on dialysis in Japan in September 2018, which is currently under review by the Pharmaceuticals and Medical Devices Agency (PMDA). Roxadustat is in Phase 3 clinical development in the U.S. and Europe and in Phase 2/3 development in China for anemia associated with myelodysplastic syndromes (MDS). Pamrevlumab, an anti-CTGF human monoclonal antibody, is advancing towards Phase 3 clinical development for the treatment of idiopathic pulmonary fibrosis (IPF) and pancreatic cancer, and is currently in a Phase 2 trial for Duchenne muscular dystrophy (DMD). FibroGen is also developing a biosynthetic cornea in China. For more information, please visit www.fibrogen.com.

Forward-Looking Statements

This release contains forward-looking statements regarding our strategy, future plans and prospects, including statements regarding the development of roxadustat, our interpretation of the pooled safety analyses and other analyses of the global Phase 3 program for roxadustat, the expected endpoints and potential standards for safety assessments of such data by the FDA and the EMA, the potential for and timing of an NDA submission to the FDA and an MAA submission to the EMA for potential marketing approval for roxadustat, the potential safety and efficacy profile of our product candidates, and our clinical, regulatory plans, and those of our partners. These forward-looking statements include, but are not limited to, statements about our plans, objectives, representations and contentions and are not historical facts and typically are identified by use of terms such as "may," "will", "should," "on track," "could," "expect," "plan," "anticipate," "believe," "estimate," "predict," "potential," "continue" and similar words, although some forward-looking statements are expressed

differently. Our actual results may differ materially from those indicated in these forward-looking statements due to risks and uncertainties related to the continued progress and timing of our various programs, including the enrollment and results from ongoing and potential future clinical trials, and other matters that are described in our Annual Report on Form 10-K for the fiscal year ended December 31, 2018, and our Quarterly Report on Form 10-Q for the fiscal guarter ended March 31, 2019 filed with the Securities and Exchange Commission (SEC), including the risk factors set forth therein. Investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date of this release, and we undertake no obligation to update any forward-looking statement in this press release, except as required by law.

Contact

FibroGen, Inc. Karen L. Bergman Vice President, Investor Relations and Corporate Communications 1 (415) 978-1433 ir@fibrogen.com



FibroGen, Inc

EXHIBIT J

S&P Global Market Intelligence

FibroGen, Inc. NasdaqGS:FGEN FQ1 2019 Earnings Call Transcripts

Thursday, May 09, 2019 9:00 PM GMT

S&P Global Market Intelligence Estimates

		-FQ1 2019-		-FQ2 2019-	-FY 2019-	-FY 2020-	
	CONSENSUS	ACTUAL SURPRISE		CONSENSUS	CONSENSUS	CONSENSUS	
EPS Normalized	(0.68)	(0.53)	NM	(0.38)	(1.00)	0.04	
Revenue (mm)	20.44	23.86	1 6.73	44.59	237.78	337.19	

Currency: USD

Consensus as of Apr-18-2019 5:22 AM GMT

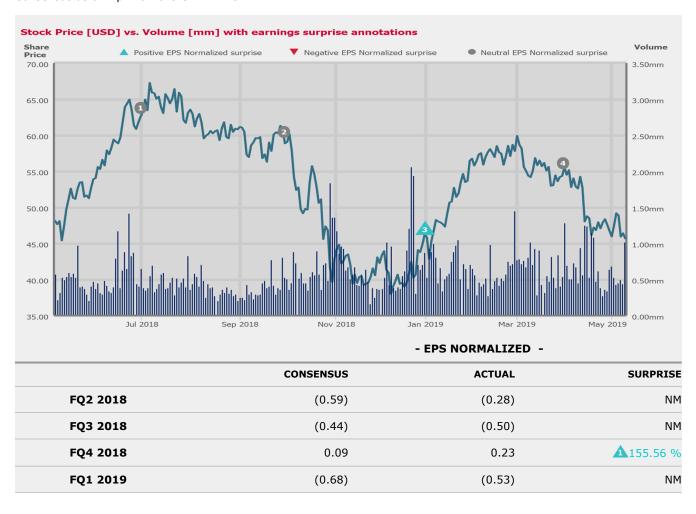


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Call Participants

EXECUTIVES

Elias Kouchakji

Senior Vice President of Clinical Development, Drug Safety & Pharmacovigilance

K. Peony Yu

Chief Medical Officer

Karen L. Bergman

Vice President of Investor Relations & Corporate Communications

Pat Cotroneo

Senior VP of Finance & CFO

Thomas B. Neff

Founder, Chairman & CEO

ANALYSTS

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Mizuho Securities USA LLC, Research Division

Geoffrey Craig Porges

SVB Leerink LLC, Research Division

Joel Lawrence Beatty

Citigroup Inc, Research Division

Michael Jonathan Yee

Jefferies LLC, Research Division

Terence C. Flynn

Goldman Sachs Group Inc., Research Division

Tsan-Yu Hsieh

William Blair & Company L.L.C., Research Division

Xiaodong Zhang

Stifel, Nicolaus & Company, Incorporated, Research Division

Presentation

Operator

Welcome to the FibroGen First Quarter 2019 Financial Results Conference Call. My name is Erin, and I will be your operator for today's call. [Operator Instructions] Please note that this conference is being recorded.

I will now turn the call over to Karen Bergman. Ms. Bergman, you may begin.

Karen L. Bergman

Vice President of Investor Relations & Corporate Communications

Erin, thank you very much. And good afternoon, everyone, and thank you for joining our call. Today, we are reporting financial results and corporate updates for the first quarter of 2019.

Joining today's call are Mr. Tom Neff, Chairman and Chief Executive Officer; Dr. Peony Yu, Chief Medical Officer; Dr. Elias Kouchakji, Senior Vice President, Clinical Development, Drug Safety and Pharmacovigilance; and Mr. Pat Cotroneo, Chief Financial Officer.

Following prepared remarks, Tom will discuss upcoming milestones, and we'll open the call to Q&A.

During this call, you may -- we may make forward-looking statements regarding our business, including our collaborations with AstraZeneca and Astellas; financial guidance; the initiation, enrollment, design, conduct and results of clinical trials; our regulatory strategies and potential regulatory results; our research and development activities; and certain other business matters. For risks and uncertainties regarding our business and statements made on the call today as well as factors beyond our control that may cause differences between current expectations and actual results, we refer you to our annual report on Form 10-K for the fiscal year ended December 31, 2018, filed with the Securities and Exchange Commission. Copies of these filings can be found in the Investors section of our website. We undertake no obligation to update any forward-looking statements whether as a result of new information, future developments or otherwise.

The format for today's call includes remarks from FibroGen's management team, and then we'll open the lines up to take your questions.

The press release reporting our financial results and business updates and a webcast of today's conference call can be found on the Investors section of FibroGen's website at www.fibrogen.com. The webcast will be available for 2 weeks from today's date.

And with that, I'd now like to turn the call over to our CEO, Tom Neff.

Thomas B. Neff

Founder, Chairman & CEO

Thank you, Karen. Welcome, everyone, and thank you for joining us. Today, we are reporting on top line adjudicated results from the 7 Phase III roxadustat studies performed by ourselves and our partners, AstraZeneca and Astellas, including the MACE and MACE+ analysis, which is an important part of the overall benefit/risk assessment regulators will perform.

These results are broken up into 2 safety pools as agreed upon with FDA and EMA. There are 4,000 patients in the pool of CKD patients who are dialysis-dependent, where roxadustat is compared to epoetin alfa and 4,300 CKD patients who are not on dialysis where we are compared to placebo.

We are also reporting results in the subgroup of incident dialysis representing patients who have recently begun dialysis and are not on ESA. This result is especially important as this setting is the most suitable for the comparison of roxadustat in the current standard of care.

In the U.S., we believe that major adverse cardiac events or MACE endpoint, defined as the time to first occurrence of death, myocardial infraction or stroke, will be the primary basis upon which the FDA will assess the safety of roxadustat.

In Europe, we believe that MACE+, which consists of the defined MACE components plus hospitalization due to heart failure or unstable angina, will be the primary endpoint for safety assessment by European regulators.

In the EU, we have agreed with regulators on a noninferiority margin. And in the U.S., we have had extensive discussions on this topic and expect to finalize standards in our pre-NDA meeting.

We discuss today some of the most important initial safety results based on a totality of data that we've analyzed to date. In addition, we want to highlight important results from other clinical measures that we are analyzing, such as change in renal function in nondialysis patients as measured by change in eGFR, efficacy of roxadustat as compared to epoetin alfa in the presence of patient inflammation and relevant quality-of-life measures in nondialysis compared to placebo.

While the FDA and EMA will make their ultimate approval decisions upon their own analyses of benefit/risk profile of roxadustat, the applicable patient populations -- nonetheless, we and our partners believe the data is strongly supportive of the efficacy and safety of roxadustat.

I would now like to walk through our MACE and MACE+ results from the adjudicated pool of Phase III data, which have been reviewed by our -- with our U.S. partner, AstraZeneca; and our EU partner, Astellas.

In dialysis-dependent CKD, in the pooled analysis, roxadustat was shown to be noninferior to epoetin alfa and MACE+ analysis. For the U.S., where there were several analyses, we believe there was no clinically meaningfully difference between roxadustat and epoetin alfa in MACE risk.

In incident dialysis, as noted above, we examined the results from the incident population who are patients in newly initiating dialysis approximately 4 months' time before they initiate anemia therapy. We believe this dialysis subpopulation is the fairest setting for comparison of roxadustat versus ESA as this period of treatment has substantially increased levels of patient mortality, where the stable dialysis population continues the twin biases of patients who have survived the incident period and are already on stable doses of ESA after dose titration.

In incident dialysis, roxadustat demonstrated superiority to epoetin alfa and time to first MACE+ analysis. And in the time to MACE analysis, there is a trend towards reduced risk for patients on roxadustat as compared to epoetin alfa.

We would highlight for you this robust result of superiority came from the 1,500-patient pool with 1:1 randomization versus epoetin alfa.

In the NDD CKD population, 4,300 patients were randomized over 3 studies conducted by AstraZeneca, Astellas and FibroGen. These studies represent the first investigation in the CKD population where median eGFR levels are much lower than prior studies. This is a study that was started after FDA restricted the use of ESAs to below hemoglobin 10 and no retreatment at levels above 10. In nondialysis, roxadustat was shown to be noninferior to placebo in time to first MACE+. In the MACE safety analysis of this population, we believe there is no clinically meaningful difference between roxadustat and placebo.

Another way to view the NDD population results is to test the ITT analysis with long-term follow-up as a majority of patients in this pool followed through the end of the study. This is a conservative way to evaluate long-term safety. In the NDD population, patients on roxadustat received treatment for longer periods than placebo patients because some of the placebo patients dropped out for lack of efficacy. Since safety data were also collected in the post-treatment period, we were able to add in ITT analysis, one, from follow-up as the majority of the patients in this pool followed through the end of the study. As to the intent-to-treat results, in multiple analyses of both MACE and MACE+, MACE-free survival and MACE+-free survival, CV MACE and CV MACE+, roxadustat was comparable to placebo. These results were below the commonly applied noninferiority margin of 1.3.

The ITT long-term follow-up analysis is one of several methods that have been discussed with the FDA to address the differential dropout rate. As to -- apart from MACE data results -- sorry, a correction I have to make which is that we have not yet spoken with FDA. These -- there is a discussion planned with the FDA about these various analyses. So it is planned to be, not has happened.

All of these evaluations help to better understand additional benefits of roxadustat apart from the MACE and MACE+ safety analyses. It is important to note that we enrolled a unique population, eGFR was from 0 to 60, including even the sickest patients with median eGFR in the study pool between 15 and 20, as large prior studies such as TREAT were enrolling patients must healthier. This is the first time a patient population this sick has been studied.

We have results in the eGFR versus placebo comparison for change in renal function over time. We evaluated whether the treatment with roxadustat could slow the rate of decline of renal function and clinically relevant matter. Evaluations were performed across all NDD/CKD populations. We also included the more conventional baseline cutoffs for nondialysis patients, meaning the patients with eGFR above 10, as well as the population eGFR above 15.

Since receiving the unblinded data after adjudication, we have completed the 1-year analysis of roxadustat versus placebo. Data evaluation in this study continues. In the 1-year data, we have observed statistically significant slower rate of eGFR decline in the roxadustat-treated patients versus placebotreated patients in the NDD pool as well as both subgroups. In the pooled analysis of eGFR change over time from the 3 NDD studies in patients with baseline eGFR above 15, they showed a treatment difference from baseline of 1.62 at 12 months. We believe the results observed over time in this analysis suggests that the roxadustat treatment may slow renal function decline in a clinically meaningful manner. We are examining the data in more detail, including stratified by level of disease progression, to understand the degree of difference and the impact of different subgroups at baseline over the longer term.

In other measures efficacy of roxadustat, we are pleased to have shown statistically significant improvement in the multiple standard quality of life measurements and to have confirmed roxadustat's efficacy in the presence of inflammation as measured by CRP where EPO requires increased doses over time. Dr. Peony Yu will describe these results in more detail later in the call.

We are on track for roxadustat's submission for U.S. NDA, September, October time period, with the European MAA submission to follow.

Let me now turn to updates regarding China. Our NDA for roxadustat was approved in December 2018 by the National Medical Products Administration, NMPA, for the treatment of anemia caused by CKD in dialysis patients. We are pleased that all clinical site inspections for the Phase III nondialysis study have now been completed by the Food and Drug Administration division, or CFDI of NMPA. And we expect the population of nondialysis CKD patients to be added to the CKD anemia indication in the roxadustat label in mid-2019.

We continue to work closely with our partner, AstraZeneca, to prepare for the launch of roxadustat in China and have much to report in terms of progress. Our partner, AstraZeneca, has already initiated the aggressive build-out of a dedicated roxadustat field sales force covering 5 regions in China at launch, which will be fully deployed by mid-2019. FibroGen China's medical affairs field staff now numbers over 30 professionals. The central market access team has been in place and active for over a year.

FibroGen is the marketing authorization holder, or MAH holder, in China that is responsible for pharmacovigilance. Our pharmacovigilance infrastructure in China, which includes a pharmacovigilance database and call center, has been active for over a quarter now. The commercial manufacturing readiness for both API and drug product is on schedule. We are confident about the third quarter China launch time frame.

A question we wanted to address is whether we will be added to NRDL List, or National Reimbursement Drug List. We are hopeful that roxadustat may qualify for consideration in 2019 by virtue of receiving market approval at the end of 2018. To be clear, only our dialysis label can be considered as nondialysis approval has not yet been received.

Many factors go into our probability of admission NRDL such as perceived unmet medical need, clinical value, pharmacoeconomic value, pricing, which is to be agreed upon between the State Medical Insurance Agency and the sponsor. We believe NRDL has critical affordability for our patients, so this is a top priority for us. Every effort is being made by the joint AZ and FibroGen team to maximize our chances of success. We expect to have a sense of whether we'll be included and at what price by sometime in October.

Finally, in Japan, our partner, Astellas, submitted the NDA for roxadustat treatment of anemia in CKD patients on dialysis to PMDA last fall. The application is currently under review, and Astellas anticipates filing the supplemental NDA for the treatment of anemia in nondialysis-dependent CKD patients in 2019.

With respect to expanded platform opportunities for roxadustat for the treatment of anemia and other disease settings, I'd like to take a moment to update you on our work with roxadustat in myelodysplastic syndromes, or MDS.

We have completed the enrollment of 24 patients in open-label lead-in portion of our multicenter, multinational Phase III study in transfusion-dependent, lower-risk patients with MDS. Encouraged by the positive results from the open-label portion, as measured by the proportion of patients who achieved transfusion independence, we have begun enrolling 160-patient, double-blind placebo-controlled portion of the study. Enrollment for the open-label portion of the China Phase II/III study is ongoing.

Turning now to pamrevlumab, our anti-CTGF antibody. We are extremely excited to see data reflecting 1 year of treatment in our ongoing Phase II study evaluating treatment of Duchenne muscular dystrophy in nonambulatory patients. The data is supportive of earlier observed trends and examines multiple parameters of disease progression, including lung function, cardiac function and muscle strength. We believe that these data would show increase in function and certain parameters will support a pivotal study and we plan to discuss with the FDA in the near future. Dr. Elias Kouchakji will discuss these results in more detail shortly.

Pamrevlumab recently received orphan drug designation for treatment of DMD. Our antibody now has orphan drug designation status in all 3 of the current indications: IPF, pancreatic cancer and DMD, and has received Fast Track designation in IPF and in pancreatic cancer.

Finally, I will briefly address financial matters here, and Pat Cotroneo, our CFO, will provide more detail later in the call. In the first quarter of 2019, we reported \$45.4 million of net loss or \$0.53 per basic and diluted share in EPS, so that's negative \$0.53 per share. As of March 31, 2019, FibroGen had \$712 million in cash.

I would now like to turn this over to Dr. Peony Yu for a discussion of the results from the CV safety pooled analysis and updates on the anemia program.

Dr. Yu, please go ahead.

K. Peony Yu

Chief Medical Officer

Thank you, Tom. For the roxadustat program, in the U.S. and EU, we are pleased to share with you the adjudicated cardiovascular pool safety analyses top line results from the Phase III global roxadustat program. We see these results supporting safety of roxadustat in CKD patients. We also see other benefits beyond hemoglobin increase.

Our MACE and MACE+. To reiterate what Tom outlined earlier in what we are disclosing on the adjudicated safety data, MACE and MACE+ composite endpoints. MACE measures the number of patients with one or more adjudicated positive MACE events, which include death, myocardial infarction and stroke. The MACE+ composite endpoint has 2 more components in addition to the MACE, in which now you also add in heart failure and unstable angina requiring hospitalization. The MACE composite endpoint is what we and our U.S. partner, AstraZeneca, discussed with the FDA for safety assessment. MACE+ is what we and our European partner, Astellas, agreed with EMA.

MACE+ have also been used extensively in safety endpoint and assessment in CKD anemia trials as well as in some diabetes trial in both Europe and in the U.S.

Now what is adjudication? And why is -- it's a part of our process? Adjudication is the process of independently and objectively applying clinical standards to consistently determine individual events qualified as MACE or MACE+ events. To maintain objectivity, independent experts in cardiology, neurology and urology who are blinded to treatment assignment revealed the patient data and adjudicate the events relevant to their specialty. To maintain data integrity, the process and documents are managed by an independent third party.

We conducted MACE and MACE+ analyses in the following patient pools: dialysis or all-dialysis; incident dialysis, which is a population of dialysis patients who are just starting out to receive chronic dialysis treatment; and as well as in nondialysis patient population.

In our dialysis pool of around 4,000 dialysis patients, based on the collective results of the various MACE and MACE+ safety analyses, we believe there is no clinically meaningful difference in MACE and MACE+ risks between roxadustat and epoetin alfa in the all-dialysis patient population and the 95% confidence interval of the hazard ratio is above -- I'm sorry, of that, 95% confidence interval of the hazard ratio is below 1.3, which is what the conventionally accepted measure in such time to analysis of MACE and MACE+.

In the incident dialysis pool, consisting of over 1,500 patients, a subpopulation of the dialysis or all-dialysis pool, which we believe offers a better setting for comparing roxadustat to epoetin alfa than the stable dialysis population, roxadustat demonstrated superiority to epoetin alfa in the time to first MACE + in this subpopulation, with fewer patients with MACE+ events was noted. In the time to first MACE analysis, there is a trend towards reduced risk for patients on roxadustat compared to epoetin alfa.

In our CKD nondialysis pool of approximately 4,300 patients, in the multiple MACE and MACE+ pool, ITT analyses conducted in nondialysis-dependent CKD patients, collectively, we believe there is no clinically meaningful difference in MACE+ and MACE+ risk between roxadustat and placebo in nondialysis patients.

Now let's put these safety findings along with the reported efficacy results in clinical context. In our last earnings call, we reported that roxadustat demonstrated efficacy in meeting the primary efficacy endpoint of change in hemoglobin from baseline to mean hemoglobin average between weeks 28 to 52 in each of the 7 Phase III studies conducted by FibroGen and our partners.

For the all-dialysis patient pool, as reported previously, not only was noninferiority achieved in primary efficacy endpoints in all-dialysis patients. Superiority in efficacy, as demonstrated by a statistically significant larger increase from baseline hemoglobin level in roxadustat-treated patients than EPO patients, was achieved in both HIMALAYAS study, which is on incident dialysis, and in SIERRAS conversion dialysis studies.

In SIERRAS, roxadustat-treated patients achieved a more physiologic hemoglobin level of 10.7 grams per deciliter versus 10.2 in EPO arm with a 33% reduction in red blood cell transfusion risk. We believe the lower achieved hemoglobin level in EPO comparator arm results from a combination of the lower target hemoglobin level on ESA label due to FDA's concern regarding ESA cardiovascular safety and EPO hyporesponsiveness in patients with inflammation, as inflamed patients with elevated C-reactive protein require higher doses of EPO than patients with normal baseline CRP levels, although they achieved lower mean hemoglobin level. And as we understand from multiple publications that there's higher risk with higher target hemoglobin when one is using ESA while higher achieved hemoglobin in EPO has been confirmed to better safety when lower doses of EPO is used.

Given the mechanism of our drug being uniquely different than EPO, being more -- at being able to achieve a more physiologic hemoglobin level should translate into benefit for patients.

Roxadustat's efficacy measured in achieved hemoglobin level and dose requirement are not affected by inflammation status unlike in EPO. This important differentiation from ESA has been observed in multiple Phase III studies including in the U.S.-based SIERRAS study, which we believe is reflective of U.S. dialysis

practice under current ESA labeling restriction. And we've also seen this differentiation in our China Phase III studies in dialysis patients.

We have also observed a reduction of red blood cell transfusion in our Phase III program. Although the roxadustat arm in conversion studies start out at a disadvantage, being exposed to patients for the first time and being compared to patients on optimized EPO dosing, the roxadustat-treated patients still show significant reduction in red blood cell transfusion risk, as measured by time to first transfusion compared to patients receiving stable maintenance doses of epoetin alfa.

Conversion patients comprise a majority in the dialysis or all-dialysis patient pool.

Yet, based on the key MACE and MACE+ analyses, we assess no clinically meaningful difference in the risk of MACE, MACE+ risk between roxadustat and epoetin alfa.

Next, the incident dialysis population is defined as patients who enter dialysis studies within 4 months of starting dialysis treatment. A vast majority of the incident dialysis patients were either ESA-naïve or had very limited prior exposure to EPO. During the transition from nondialysis to dialysis in the first 4 months of dialysis treatment, patients suffer from mortality and hospitalization rate at twice those of dialysis patients who survived the first year of dialysis treatment.

What's also relevant to roxadustat is that initiation of dialysis often also coincides with the initiation of anemia therapy. We and our partners are very happy with the result of superiority to epoetin alfa in the time to first MACE+ and a favorable trend towards reduced risk for patients on roxadustat compared to epoetin alfa in time to first MACE analysis in the incident dialysis patient populations.

We believe roxadustat's favorable results in incident dialysis compared to EPO could enable a safer treatment of anemia in CKD patients initiating and continuing dialysis treatment.

Turning to CKD patients not on dialysis. In the CKD pool analyses from the 3 nondialysis studies, roxadustat both consistently raised hemoglobin levels to a mean hemoglobin of 11 gram per deciliter in the roxadustat-treated patients and significantly reduced red blood cell transfusion compared to placebo. This is very important for patients to preserve their ability to have kidney transplant later down the road if they need to. Importantly, roxadustat has shown the potential to preserve renal function as there was a statistically significantly smaller decline in eGFR in roxa-treated patients than placebo, with a treatment difference of 1.62 in eGFR units when measuring change at 1 year from baseline in patients with baseline eGFR of 15 or higher. P value is 0.0001 or a reduction of decline by 38% in eGFR relative to placebo arm.

We also observed statistically significant improvements in the various quality of life endpoints at 12 weeks from baseline, including the SF-36 Vitality subscale with P value that has 0.0002; SF-36 Physical Functioning subscale P value of 0.0369; FACT-AN Anemia subscale with P value of 0.0012; FACT-AN Total score P value of 0.0056; EQ-5D-SL VAS score with P value of 0.0005 in CKD patients not on dialysis.

Putting together these and other important potential clinical benefits with the safety results that we have seen in comparison with EPO, which is a gold standard for safety measurement; and in comparison to EPO, which is the current standard of care in dialysis but have some limitations, along with the convenience of a pill when treating patients with roxadustat to make treatment much, much more accessible than parenteral route of ESA, we are excited about the potential of roxadustat as an innovative new therapy for CKD patients. We hope this provides some helpful context for you in understanding the significance of the safety top line results announced today.

Tom has already touched on the status of our U.S./EU submission plans. We and AstraZeneca will be in discussion with FDA on NDA submission plan, which we are targeting for September/October time frame. We are also supporting Astellas' MAA submission to EMA to be submitted thereafter. For China, in April, CFDI inspected our China Phase III CKD nondialysis study sites. We expect that the roxadustat label on CKD anemia there will be expanded midyear to include nondialysis as well as dialysis patients.

As Tom mentioned, we are excited about roxadustat's opportunity for market access via this year's NRDL election process in China.

In Japan, the NDA on roxadustat for treatment of anemia in dialysis-dependent CKD patients submitted by our partner, Astellas, in September 2018 is now under review. We anticipate the Japan NDA decision later this year.

For the treatment of anemia in MDS patients, we have an ongoing Phase III study in transfusion-dependent, lower-risk MDS patients in the U.S., Europe and Asia, plus another study, which is Phase II/ III in non-transfusion-dependent MDS patients in China. Each has an open-label run-in period. Anemia in MDS is notoriously difficult to treat, and we are striving to make a difference for MDS patients with roxadustat. We have completed enrollment of the first 24 patients in the open-label portion of the U.S./ European study. We and our partners are encouraged by the available results as there were a large proportion of transfusion-dependent patients able to achieve transfusion independence endpoint. And we have already started dosing in the double-blind portion of the U.S./European Phase III MDS study.

Finally, we are on track to start our first clinical trial in chemotherapy-induced anemia with roxadustat. It's a Phase II study in the U.S. to be started shortly in 2019. I believe that all of us are aware and would like to do something about the under-treatment of anemia in patients who have undergone chemotherapy.

I'd like to now turn the call back over to Tom.

Thomas B. Neff

Founder, Chairman & CEO

Thank you, Peony. Dr. Elias Kouchakji will now provide an update on pamrevlumab, including additional details on our DMD data, and update us on clinical development activities for pancreatic cancer and for IPF. Elias, please go ahead.

Elias Kouchakji

Senior Vice President of Clinical Development, Drug Safety & Pharmacovigilance

Thank you, Tom. I will start with the Duchenne muscular dystrophy, as Tom mentioned. In mid-March of this year, all 21 patients completed 1-year treatment with pamrevlumab in our Phase II open-label nonambulatory Duchenne muscular dystrophy study. Soon after, we initiated an administrative analysis of the data in the early second quarter of this year. This is in order to inform our clinical development strategy and we reviewed this study data with key opinion leaders who are experts in the study of the critical function we tested in this study.

Starting with the pulmonary function test, the complete 1-year results indicate a potential reduction in the rate of decline in FVC percent predicted from baseline in our study population, especially when compared to the data published in 2016 by [Maher Horicoti] in 2019.

As for the cardiac function test, the result, as measured by LVEF, left ventricular ejection fraction, the data suggested a positive mean percent change from baseline while the published data by McDonald in 2018 showed a mean decline of approximately 1% from baseline in 1 year.

Additionally, we've measured the cardiac fibrosis scores, and we collected the data. The published data by Tandon in 2015 showed a strong correlation between the cardiac fibrosis with LVF. Our data from the MRI fibrosis score suggests a similar correlation.

Similarly, in some of the muscle function tests, the result of this test in the upper arm showed the mean change from baseline was smaller than the published data by [Raikoti] in 2019.

Based on these results and advice we received from our expert, we are planning to share these results with FDA to develop our clinical development plan for Duchenne muscular dystrophy.

Moving forward with our other indication. We are planning on beginning enrolling in the Phase III double-blind placebo-controlled of pamrevlumab as neoadjuvant therapy for non-resectable locally advanced pancreatic cancer in the second quarter of 2019. We intend to enroll approximately 260 patients. Randomization 1:1 to receive either pamrevlumab in combination with gemcitabine and nab-paclitaxel or chemotherapy with placebo.

Also in the second quarter of 2019, we are on track to begin enrolling our double-blind placebo-controlled Phase III study of pamrevlumab in approximately 500 IPF patients. The primary efficacy endpoint is a change from baseline in forced vital capacity.

We are grateful for the opportunity represented by pamrevlumab in providing a needed therapeutic option for each of these 3 serious and progressive indications: Duchenne muscular dystrophy; pancreatic cancer; and idiopathic pulmonary fibrosis.

Thank you for listening. Tom, I'll turn the call to you.

Thomas B. Neff

Founder, Chairman & CEO

Thank you, Elias. Pat Cotroneo, our Chief Financial Officer, will now discuss financial highlights for the first quarter of 2019. Pat, please go ahead.

Pat Cotroneo

Senior VP of Finance & CFO

Thank you, Tom. As announced today, total revenue for the quarter ended March 31, 2019, was \$23.9 million as compared to \$31.9 million for the first quarter of 2018. For the same period, operating expenses were \$72.7 million, and the net loss was \$45.4 million or negative \$0.53 per basic and diluted share as compared to operating expenses of \$72.5 million and a net loss of \$41.4 million or negative \$0.50 per basic and diluted share for the first quarter last year.

Included in operating expenses for the quarter ended March 31, 2019, was an aggregate noncash portion totaling \$20.2 million, of which \$16.4 million was the result of stock-based compensation expense, as compared to an aggregate noncash portion totaling \$12.5 million, of which \$10.9 million was the result of stock-based compensation expense for the same period in the prior year.

At March 31, 2019, FibroGen had \$712.7 million in cash, restricted time deposits, cash equivalents, investments and receivables. As previously stated, our considered judgment is that the roxadustat NDA and MAA will be filed this year, which will trigger approximately \$192.5 million in anticipated milestone payments, of which the vast majority are associated with these filings.

Thank you, and I will turn the call back over to Tom.

Thomas B. Neff

Founder, Chairman & CEO

Thank you, Pat. With the updates reported to you today, we advanced a number of critical events in the coming months. It is our privilege to have shared with you today roxadustat's CV pooled safety analysis results that we believe support submitting the NDA for both NDD and DD indications, treatment of dialysis-dependent and nondialysis-dependent CKD, to the FDA in September or October 2019.

In Europe, our partner, Astellas, anticipates submission of the MAA for dialysis-dependent and nondialysis-dependent CKD later in 2019 November, December. And in China, we expect to add nondialysis-dependent CKD patients to the roxadustat label upon approval anticipated in mid-2000 -- Q3 2019. In Japan, Astellas is expecting a decision on NDA approval for roxadustat in dialysis-dependent CKD in fourth quarter of 2019.

For pamrevlumab, we look forward to updating you on our advancement to Phase III in LAPC and IPF and to further findings from our ongoing Phase II study in DMD nonambulatory patients.

With that, let me turn this back to Karen to begin the question-and-answer period.

Karen L. Bergman

Vice President of Investor Relations & Corporate Communications Thank you, Tom. Erin, please open up the lines for questions.

Question and Answer

Operator

[Operator Instructions] Your first question comes from Michael Yee with Jefferies.

Michael Jonathan Yee

Jefferies LLC, Research Division

Tom and Peony, can you be very clear for us? I think there's some confusion around whether you are statistically noninferior in dialysis and nondialysis on the MACE analysis, which is what is required for FDA? Can you confirm that or discuss that? And if you can also give us the hazard ratios for dialysis and nondialysis on MACE, that would be very helpful.

Thomas B. Neff

Founder, Chairman & CEO

Okay. So Michael, there's 2 parts to this answer. One is that in the European market, we are doing MACE +, where we have a statistical noninferiority margin, a single margin identified, and we are noninferior in both measures. In the U.S., there are multiple noninferiority margins that are under discussion. These are reflecting the fact that was not incident dialysis and with the nondialysis-dependent CKD patients, we are essentially addressing new indications that have not been investigated previously. So that's incident dialysis and the CKD dialysis. In discussions with our partner, they are very mindful of the phrase of totality of evidence. And so they encouraged the idea that we address this in the form of the evaluation of results versus MACE, where we did not see any clinically meaningful difference, means that it met the safety standards that people were looking for and that's why people are moving forward.

Michael Jonathan Yee

Jefferies LLC, Research Division

So to be very specific, in dialysis and nondialysis on MACE, are you trending the right way? Are you trending positive? What do you mean by not clinically meaningful differences?

Thomas B. Neff

Founder, Chairman & CEO

Yes. I think the message there is we're trending favorably. But at the same time, we have to yet agree with our regulator on specific analyses to be done. There are back and forth discussions.

Michael Jonathan Yee

Jefferies LLC, Research Division

Okay. So it's trending -- it was trending positive, but you just don't have an -- or you just don't have an agreement on what the definition of which analysis you would like to have, but it is trending positive.

Thomas B. Neff

Founder, Chairman & CEO

Michael, I think that's a very fair way to say it.

Operator

And your next question, that comes from Andy Hsieh with William Blair.

K. Peony Yu

Chief Medical Officer

Before Andy, may I add to Michael's response, to Michael Yee's question? I just -- I don't know whether we made it very clear that when Tom and I used the number 1.3, we are talking about -- we are not talking about a hazard ratio. I want to make it absolutely clear that the hazard ratio for the MACE+ in the incident

dialysis is way below 1. And in -- also, it's below 1 in dialysis, okay? And the upper bound of the 95% confidence interval, when you are below 1.3, that has been a commonly accepted statistical standard for noninferiority.

And for us to state that we are superior in time to MACE+ analysis in incident dialysis, what I mean is the upper bound of the 95% confidence interval is less than 1. And we have a -- when you compare the hazard between roxadustat to that of epoetin alfa, we have a very significant P value. So I hope this helps. Michael, does this answer your question?

Michael Jonathan Yee

Jefferies LLC, Research Division

Okay.

K. Peony Yu

Chief Medical Officer

Okay. Andy?

Operator

Andy, perhaps you're muted.

Karen L. Bergman

Vice President of Investor Relations & Corporate Communications

Andy, are you still on the call with us? This is Karen. I think we lost him.

Operator

Your next question comes from Joel Beatty with Citi.

Joel Lawrence Beatty

Citigroup Inc, Research Division

This question is on the 2 pooled noninferiority MACE analyses required by FDA. Was there a prespecified statistical analysis plan agreed to with FDA?

K. Peony Yu

Chief Medical Officer

So Joel, we have had discussions with the FDA on how they -- on the different methods for -- of statistical evaluation of safety endpoints. We believe that we have collected the data that the FDA would like to see. And -- but we wanted to be cautious as -- in stating our agreement with the FDA because as we -- those of us who have interacted with the FDA, oftentimes, the reviewers would like to have the -- would like to look at the totality of evidence, looking at both the safety as well as efficacy. And they -- but the term that is used very commonly is called -- it's a review issue. So it's not an issue, but it is -- if I were the reviewer, I would like look at -- like to look at all the data before I would commit to a decision of -- on a drug. And so I hope that answers your question.

Joel Lawrence Beatty

Citigroup Inc, Research Division

Okay. Understood.

K. Peony Yu

Chief Medical Officer

And then to ensure alignment, we will be discussing with FDA and in our upcoming pre-NDA meeting to make sure that our preparation of the NDA package will provide the information that -- in a way that is efficient for FDA to review.

Joel Lawrence Beatty

Citigroup Inc, Research Division

Okay. And then a question on the nondialysis MACE analyses. Did the event rate compare favorably to the comparator arm? And how -- in that analysis, how does it take into consideration the differences in the dropout rate?

K. Peony Yu

Chief Medical Officer

Yes. We do -- so first of all, Joel, that's a good question. So we have -- because our drug is so efficacious and so well tolerated, patients really like staying on our drug. Now -- plus, we all know that placebo doesn't work too well, so -- however, this is -- I want to go back and remind everyone that this is a double-blinded study. And so even -- so many patients -- these patients -- in other words, patients are not -- do not have the treatment assignment information. We have many patients who are on placebo and on roxadustat who remain in the studies to enable a long-term efficacy and safety evaluation. And even we did see a high -- a somewhat higher dropout rate in placebo-treated patients.

However -- and to have some anticipation this could happen, we have collected safety data on patients during the post-treatment period. And that's why we are able to conduct the ITT analysis. And this will be -- of course, the final assessment in -- and the statistics will be discussed with the FDA.

And I just wanted to share that in the -- so what we have mentioned in the ITT analysis, in the nondialysis patient population, it is -- will be considered a relatively conservative analysis. And the fact that we had -- we are able to show noninferiority to placebo under such conditions really illustrates the strength of our drug's safety. And I wanted to also remind us that placebo is considered the gold standard for safety.

Thomas B. Neff

Founder, Chairman & CEO

Okay? Go ahead. Andy, are you there?

Tsan-Yu Hsieh

William Blair & Company L.L.C., Research Division

Yes, I'm here. Can you guys hear me?

Thomas B. Neff

Founder, Chairman & CEO

Yes.

Tsan-Yu Hsieh

William Blair & Company L.L.C., Research Division

Yes. I'm sorry, Tom, and to the team that I pressed the wrong button, so yes, it caused a little confusion so I apologize. So my question has to do with just looking at it from a bigger-picture perspective. You have -- on the MACE perspective nonclinically -- well, I guess, not -- no clinical difference between both arms, roxadustat versus EPO, roxadustat versus placebo. But this is -- from a -- I don't know if this is a correct way to think about it, from transitive property of equality, we know that placebo is not -- from a clinical perspective, does not equal to EPO. So how do you kind of think about this discordance and with what you just disclosed on the call?

Thomas B. Neff

Founder, Chairman & CEO

Well, so let's do this in a simpler groundwork on, which is MACE+. And I'm doing this because we have very defined criteria of MACE+. The findings are, with incident dialysis pool, you have statistically significant advantage over ESA; with the entire dialysis pool, noninferior; and then in the NDD nondialysis pool, you have noninferior. So you have these comparisons. We think of the nondialysis pool comparison to placebo, it's essentially similar. This -- the idea there is that it's hard to argue that there's an incremental

safety risk because placebo is what happens with CKD patients every day right now. They don't have medicines. So it's not as if you can infer an incremental statistically proven risk in nondialysis.

In the dialysis pool, the broader population, noninferior and in the incident population, which we think is the unbiased comparison, we have statistical superiority. We don't expect that MACE will be particularly different than this. It's just that with U.S., we have an agreement with our partner, AstraZeneca, to evaluate on a totality of evidence basis. So it makes it harder to sum this up in 1 sentence or 2 sentences. It's sort of a pretzel logic challenge to try to describe this accurately, but I think you can sort of look at the MACE+ results. And from our point of view, if we thought the MACE results were going to be a lot different, we would say so. But it doesn't seem that way. It seems very similar.

So I would say, with the U.S., attributed to the fact that we do not have a single agreed endpoint -- one of the questions we asked with these newly defined populations in incident dialysis and in CKD was whether or not the entire analysis, the entire risk/benefit analysis should work a little differently than in the conversion dialysis patients that have been using EPO forever. And the FDA basically said, "That's a review issue. You need to spend some time showing us the benefit/risk analysis that you see from your data."

K. Peony Yu

Chief Medical Officer

I -- yes. So Tom, may I supplement this a little bit?

Thomas B. Neff

Founder, Chairman & CEO

Sure.

K. Peony Yu

Chief Medical Officer

I apologize if we used too much of this statistics mumbo jumbo. But I will -- I just wanted to add, even though we are saying that there's no clinically meaningful difference in MACE and MACE+ in dialysis, I'm just going to give one example, okay?

And even though we are saying that, it is a very conservative way of expressing our data. In absolute terms, we have -- for example, in our dialysis pool, we have fewer patients. Now we look at on treatment analysis, and there are fewer patients who died on the roxadustat compared to EPO. We have fewer -- numerically fewer patients with a MACE event or with MACE+ events. So that's sort of I'm trying to give you a little color to what we are saying. It doesn't -- but I hope this is helpful.

Tsan-Yu Hsieh

William Blair & Company L.L.C., Research Division

So just kind of digging deeper and helping us kind of understand the totality of data. Different components, death, MI, stroke. On top of that, unstable angina leading to a hospitalization, heart failure. Can you confirm that all of these measures are trending in the right direction? Or maybe there are some that's not. Maybe can you comment on that?

Thomas B. Neff

Founder, Chairman & CEO

So with the MACE+ data, I believe we have numeric advantage in each category. So there's 5 categories.

K. Peony Yu

Chief Medical Officer

Each and single one of them, Tom.

Thomas B. Neff

Founder, Chairman & CEO

Every one of them, we have a numeric advantage over ESA. Is that clearer now?

K. Peony Yu

Chief Medical Officer

Numeric advantage, meaning lower.

Thomas B. Neff

Founder, Chairman & CEO

Fewer events in roxa versus ESA in deaths. Fewer events in roxa versus ESA in myocardial infarction. Fewer strokes in roxa than ESA. Fewer unstable angina hospitalizations. Fewer congestive heart failures resulting in hospitalizations.

Tsan-Yu Hsieh

William Blair & Company L.L.C., Research Division

Yes. That's actually super helpful. And just one last question about the quality of life measures. 12 weeks into that, given that this is a chronic condition, is that clinically relevant? Or should you be looking at a longer time frame?

Thomas B. Neff

Founder, Chairman & CEO

Peony, what was the link with quality of life studies?

K. Peony Yu

Chief Medical Officer

Yes. So the quality of life number that I quoted was at 12 weeks. Quality of life measures is actually quite -- is quite difficult to measure over long term. And because you have -- you wanted to measure in the same patient population that you start out the study with. And also, on the subjective measures that where a patient report to you how they feel, when you carry it over a much longer period of time, there's patients tend -- not only patients, I may have forgotten how things -- how bad things were like a couple months ago. And so generally, it is reasonable. 3 months is a very reasonable period to record patient-reported outcome.

Operator

And your next question comes from Terence Flynn with Goldman Sachs.

Terence C. Flynn

Goldman Sachs Group Inc., Research Division

Maybe just a follow-up. I think that your answer to the last question regarding the dialysis population was pretty clear. But in terms of the nondialysis comparison of roxa versus placebo, I guess, I'm still a little bit confused in terms of how the -- I understand you didn't have a prespecified comparison. You're looking at a number of different ways. But could you maybe just walk through how those event rates compare on MACE for roxa versus placebo across the different analyses? Were there -- did they all line up? Were they all favorable? Was there anything out of line?

And then when you look at the separate studies, again, I remember back from the [Amanta] studies, they had one trial that they showed fewer events and one trial they actually had more events in the nondialysis setting. So again, was there consistency across the 3 studies that you pooled as well?

Thomas B. Neff

Founder, Chairman & CEO

Yes. So Terence, we recognize that this is a terribly difficult area to state in a succinct manner for a call like this. Having said that, in thinking about how to describe the situation most effectively, we decided to describe the ITT results. This is MACE, MACE+, MACE CV, time to MACE+, time to MACE. So there's

several different measures. And in each case, the result of the analysis was at a ratio below 1.3, which is a standard noninferiority comparison in ITT.

And so when I say below 1.3, I mean like 1.18 or 1.21 or 1.27 or 1.28. Not above 1.3, but below 1.3. And I know, speaking as someone involved in this partnership for a long time, that people in each of our partners' executive management group, great confidence and strength in seeing these results because these are -- even though these maybe aren't the measures that will ultimately be the ones that are evaluated, they are an ultimate safety evaluation standard that FDA usually asks for, whether you pose it or not. So everybody felt like this is something that's very descriptive and very informative. I would hesitate to do anything else beyond talking about the ITT results because we do not have a specific agreement with FDA on method of analysis. And as such, it's a little presumptuous.

And I think the challenge for any of these statistics that would be like OT-7 or OT-28 or whatever, is that you have a placebo dropout rate that's very different than the roxa stay-on study rate. There is agreement from regulatory body that we can make statistical adjustments. We've gotten that in print from our reviewers. And there's certain things like covariance or IPCW adjustments that have been suggested as ways that there's an acknowledgment this placebo dropout rate is an issue that needs to be evaluated.

Peony, why don't you go ahead from there?

K. Peony Yu

Chief Medical Officer

Yes. So FDA specifically suggested for us to do exposure-adjusted safety analysis. So if you have more patient exposure time on one arm than another, how do you compare the number of patients who have how many events? And so when we -- so that's why the ITT evaluation is one of the ways that we make such comparison.

Another way will be exposure-adjusted to match the follow-up time on the 2 arms. When we do that, we again see very, very reassuring safety data. And there's no -- and we see there -- this certainly looks noninferior in our assessment.

Terence C. Flynn

Goldman Sachs Group Inc., Research Division

Okay. Can I maybe just ask 2 follow-ups?

Thomas B. Neff

Founder, Chairman & CEO

Sorry. You get one more. Terence, you get one more. What is it?

Terence C. Flynn

Goldman Sachs Group Inc., Research Division

Okay. Sure. Just again, so below 1.3, so that was for each of the 3 studies? Just to be crystal clear on that. Or that was on a pooled basis when we're talking about the nondialysis population?

Thomas B. Neff

Founder, Chairman & CEO

This is all nondialysis and its evaluations, MACE, MACE+, MACE CV. Peony, do you want to add to that?

K. Peony Yu

Chief Medical Officer

Yes. So Terence, so the agreement we had with our regulators is that for MACE and MACE+ type of analysis will be based on pool analysis across the 3 studies and that is...

Thomas B. Neff

Founder, Chairman & CEO

The 3 nondialysis.

K. Peony Yu

Chief Medical Officer

The 3 nondialysis studies and with a total sample size of about 4,300 patients.

Terence C. Flynn

Goldman Sachs Group Inc., Research Division

Okay. So you can't give us any more detail about the individual studies, I guess, at this point in terms of what the individual numbers look like. Like, if they -- I'm just trying to understand if they're consistent across the 3 studies.

K. Peony Yu

Chief Medical Officer

Okay. So Terence, there is consistency across the 3 studies in that we met primary efficacy endpoints in all 3 studies, in hemoglobin endpoints and that we achieve transfusion superiority, which is clinically very important. And each of the individual -- none of the -- each of the individual study, safety trends were -- overall safety trends were acceptable. And I just wanted to share that for MACE and MACE+ events, you need a certain powering statistics -- adequate statistical power to have meaningful comparison. So this is why we are reporting the pool result rather than individual study result.

Operator

And your next question comes from Geoffrey Porges with Silicon Valley Bank Leerink.

Geoffrey Craig Porges

SVB Leerink LLC, Research Division

Appreciate all the color that you're providing. Peony, could I ask you to pivot to the dialysis population? And you've broken out the incident dialysis population, where you seem to have superiority on MACE+ and trended benefit on MACE. Could you give us a sense of what you see in the stable dialysis patients? Particularly, provide us reassurance that the number of -- or whatever, however you care to measure it, the number of deaths, MIs and strokes in the stable dialysis patients who were switched to roxadustat, still favors roxadustat. Because obviously, you don't have the same power or same apparent benefit in the pooled dialysis as you do in the incident.

K. Peony Yu

Chief Medical Officer

Okay. Geoff, yes, I wanted to -- first of all, I think we agree that the conversion dialysis study design is biased against the study drug. But even so, when we look at subgroup analysis of the -- between incident dialysis versus the stable conversion dialysis, we are quite comfortable with the safety result when looking at MACE and MACE+. We -- does that help?

Geoffrey Craig Porges

SVB Leerink LLC, Research Division

Could you provide the same -- is the rate of deaths, MI and stroke in that population lower in the roxatreated patients?

K. Peony Yu

Chief Medical Officer

Yes. So I don't have the exact number sitting in front of me, but I would think that, from memory, they seem to be not that far off from one another.

Geoffrey Craig Porges

SVB Leerink LLC, Research Division

Okay. Peony, could I just follow up? And could you just talk a little bit about...

K. Peony Yu

Chief Medical Officer

We have a lot of numbers here, Geoff.

Geoffrey Craig Porges

SVB Leerink LLC, Research Division

Yes, I understand. Could you just talk about the overall rate of events that you've seen compared to expectations? And also, whether there are any geographic variances in the comparison depending upon geography, North America, Europe, et cetera?

Thomas B. Neff

Founder, Chairman & CEO

Geoff, I'm sorry. Just a second. I think there's -- Geoff, I want to get clarity on the question you just asked, but I think Peony wants to clarify one thing. Peony, go ahead.

K. Peony Yu

Chief Medical Officer

Yes. So Geoff -- yes, so we -- when we tested the -- yes, when we tested the non-bio, I wanted -- even though I'm not giving you exact number of patients for each category, right, but I am willing to share with you that in the subgroup analysis, when we tested time to -- for example, time to MACE+ and MACE, roxadustat was at least noninferior to epoetin alfa even in the conversion stable dialysis patients.

Geoffrey Craig Porges

SVB Leerink LLC, Research Division

So you mean if you take the subgroup of incident patients away, the remainder pool was tested as noninferior consistently?

K. Peony Yu

Chief Medical Officer

Correct.

Geoffrey Craig Porges

SVB Leerink LLC, Research Division

So that's the clarification.

Thomas B. Neff

Founder, Chairman & CEO

Now Geoff, please state the geography question again. It surprised us. I don't think I heard the whole thing.

Geoffrey Craig Porges

SVB Leerink LLC, Research Division

I just want to -- could you just comment on the overall rate of events that you've observed compared to expectations? And then whether there were any variations in the comparison between the different arms in the -- when you look at the subsets by geography?

K. Peony Yu

Chief Medical Officer

Geoff, we're at this -- we are still on the -- releasing the top line results. The fine granular geographic subgroup analysis and more detailed analysis are -- still needs to be conducted. But we'll plan to -- between now and NDA submission, it will be completed before then.

Geoffrey Craig Porges

SVB Leerink LLC, Research Division

Okay. And the overall event rate or rates?

Thomas B. Neff

Founder, Chairman & CEO

The question was, do you observe any difference in overall event by geography?

K. Peony Yu

Chief Medical Officer

We have not done that subgroup analysis by geography yet.

Thomas B. Neff

Founder, Chairman & CEO

Okay. Yes. Thank you.

Operator

And your next question comes from Difei Yang with Mizuho Securities.

Difei Yang

Mizuho Securities USA LLC, Research Division

I'll apologize upfront. I may be a little slow. I'm trying to get some of the answers. So Tom and Peony, maybe you could help me think about 3 patient populations. There's the DD, NDD and incident dialysis. Is incident dialysis patient population as a possible indication in the U.S.? I'm focusing on the discussion just for U.S. filling alone. Are we dealing with 3 patient populations in terms of getting approval? Or are we dealing with 2, really, either it's DD or NDD?

K. Peony Yu

Chief Medical Officer

So Difei, thank you. That's a very good question. We have already -- we have had initial discussion with the FDA regarding the 3 patient populations and the understanding is that the incident dialysis population is one that is -- I mean, the understanding is that all 3 patient populations for indication are under discussion that will be -- that is ongoing with the FDA. And we believe that the results will help drive the decision.

Difei Yang

Mizuho Securities USA LLC, Research Division

Okay. Okay. Now for the indication in the U.S., if we just think about DD and NDD for now, for the MACE status, now we can forget about the MACE+ situation. Just for the MACE measurement, have you reached a statistical noninferiority on -- against either placebo or EPO?

K. Peony Yu

Chief Medical Officer

So Difei, we -- so whether you would reach statistically significant in noninferiority, it really depends on what the noninferiority margin is. And in Europe, we are more clear on the noninferiority margin, and we believe that we have achieved that.

And for -- now for the incident dialysis, the nice thing about achieved superiority is that no matter what the noninferiority margin it is, once we can demonstrate superiority, we have already crossed it.

And we are using the conventional standards of noninferiority, which is widely published for assessment of CKD anemia and have previously been used by U.S. regulator for assessment of cardiovascular safety in similar types of composite endpoints that we -- that standard has been 1.3 for upper bound of 95%

confidence interval. If we use that standard, the answer is yes, we have achieved noninferiority. And so the reason that we are not as explicit in saying that is because we got -- we wanted to be transparent when we state what we mean by noninferiority. I hope this helps.

Difei Yang

Mizuho Securities USA LLC, Research Division

This is very, very helpful. So then if I could ask a question on quality of life measurement. Do you see superiority or nonsuperiority on the ID and DD patient population? I think NDD, you said you've achieved superiority. Is that the right understanding?

K. Peony Yu

Chief Medical Officer

So Difei, the reason that we focus on testing quality of life in nondialysis is that we are testing against placebo, and we do superiority testing. In dialysis, it's not as meaningful because when we are comparing against an active comparator, that clearly does not have a label for quality of life. I mean, even if you're noninferior, what does that mean? It's not going to get us a label. And trying to go for superiority, that doesn't make sense either. So that's why we focus our quality of life measures in the nondialysis patient population.

Thomas B. Neff

Founder, Chairman & CEO

Just to be clear, we only tested quality of life in nondialysis, the 4,300 patients in nondialysis, not in dialysis. Okay?

Difei Yang

Mizuho Securities USA LLC, Research Division

Okay. That's very helpful. So my final question is that it sounded like you plan to file NDA in September, October time frame. But before then, there will be FDA meeting. Would you update us? Or do you have plans to update investors before the NDA submission when you have more clarifications on the data analysis, et cetera?

K. Peony Yu

Chief Medical Officer

So Difei, I'm looking at my colleague heading regulatory, and we normally do not do a press release before or at -- necessary when we go see the FDA. However, we will certainly update our investors when we submit NDA. And I see Wayne nodding his head.

Thomas B. Neff

Founder, Chairman & CEO

And I would also say that if there is a meaningful change in the time line assumptions, which now are September, October submission time, we will let investors know.

Operator

And your next motion comes from Adam Walsh with Stifel.

Xiaodong Zhang

Stifel, Nicolaus & Company, Incorporated, Research Division

This is Edwin Zhang on for Adam. Congrats on the data. A couple of questions for me. First, based on this MACE data, how do we think of the label language if approved? Are we confident to avoid a black box?

K. Peony Yu

Chief Medical Officer

Adam, thank you for...

Thomas B. Neff

Founder, Chairman & CEO

Not Adam. Edwin.

K. Peony Yu

Chief Medical Officer

Oh, you're not -- oh, you're Edwin. Okay. Sorry, Edwin. So thanks for the questions. Now when -- now what FDA puts on the label is something that they -- that we may not have much control over, except that we have developed a package that we'll target a certain label. And so we -- FDA has advised us that the evaluation of efficacy, primary efficacy, will be based on individual studies, and we have checked that box. And the evaluation of safety is FDA may -- will look at various aspects of safety. And based on what we have seen, we are pretty comfortable with safety. This adjudicated composite safety endpoint was something that we have discussed with the FDA. And at this time, we are quite happy with the result.

The fact that we believe that the CV safety endpoints in our studies in the nondialysis, when compared to the gold standard of placebo, we are now seeing increased risk that makes me think that we have a chance of avoiding some of the -- certain of those terms that is currently on the EPO label. However, this is what we are targeting when we selected placebo as a comparator. But at the end, the assessment is -- really depends on the medical reviewer at the FDA. And there will -- if there were an Advisory Committee, then there would be input from the Advisory Committee if the FDA chooses to.

Xiaodong Zhang

Stifel, Nicolaus & Company, Incorporated, Research Division

Okay. In term of the totality of the data, the additional positive benefit in NDD is really impressive, like a slower eGFR decline, the quality of life or even efficacy in the inflamed patient, which are not seen in the EPO treatment. What do you think of -- as the agency will look at this benefit from roxa, do you think that we will have to open a larger market for roxa in DD?

K. Peony Yu

Chief Medical Officer

Yes. So this is a great question. We have discussed with the FDA on how to look at the drug, and the FDA has explicitly advised us that benefit will be taken into consideration as they evaluate each drug based on the combination of benefit/risk. And we are hopeful of being able to reach more CKD patients in need with this highly assessable drug that is just a pill and not have to go drive to the doctor's office regularly to get shots.

Xiaodong Zhang

Stifel, Nicolaus & Company, Incorporated, Research Division

And when do we expect to see the full MACE data?

K. Peony Yu

Chief Medical Officer

We are -- that's a very good question. Right now, we are sharing with you some very, very top-level results. And we'll be in discussion with our partners to -- so there are 2 key places where we'll be sending the pooled MACE data. One is to the health authority to try to get the drug approved and to submit to major conferences. And since we just got the data, we are in discussions with partners on which conference and which journal to submit manuscript to. This will be a lot of fun.

Xiaodong Zhang

Stifel, Nicolaus & Company, Incorporated, Research Division

Can I ask for one question on DMD? I don't want it overshadowed by the MACE question.

Thomas B. Neff

Founder, Chairman & CEO

Thank you.

Xiaodong Zhang

Stifel, Nicolaus & Company, Incorporated, Research Division

When are we going to see the data, the DMD data? And from the next study, what is your planed dosing regimen, the new point? And what kind of control arm you will use?

Thomas B. Neff

Founder, Chairman & CEO

Yes. So I think there is a lot to talk about here. An important idea is the left ventricular ejection fraction, LVEF. We have positive numbers. This is sort of a big deal, right? But in terms of what's going to happen next, I will let Dr. Elias Kouchakji speak to his plan.

Elias Kouchakji

Senior Vice President of Clinical Development, Drug Safety & Pharmacovigilance

So as we talked and then mentioned by Tom, that is we are -- first is we are looking to go and talk with the FDA about the next step in the -- with this data. And at the same time, we are looking to collect this additional natural disease history data, which is very important. And from there, we, hopefully soon after, we will be publishing our data and have this one, inferior disease arm -- or data that we collected in this patient population. We are looking for the earliest conference as possible that is we could putting some of our data out, which is most likely will be done in the World Muscle Society.

Operator

Okay. And we have no further questions at this time, so I would like to turn the call back over to Tom Neff for closing remarks.

Thomas B. Neff

Founder, Chairman & CEO

Thank you all for joining us on this call today. These data represent the culmination of many, many years of hard work on the part of our team in FibroGen, some cases, measuring a decade or more. Thank you all for your dedication to and belief in our program. We actually believe we have very good data. I also would like to thank all the physicians, investigators and patients who participated in the clinical development programs, our collaboration partners and our investors for patience and continued support.

We look forward to keeping you updated on our progress throughout 2019. I'd like to wish everyone a good afternoon and evening. Thank you for joining our call.

Operator

Thank you, ladies and gentlemen. This concludes today's conference. Thank you for participating. You may now disconnect.

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EXHIBIT K

Jefferies

EQUITY RESEARCH FibroGen Inc (FGEN)

We spoke with mgmt, Roxa event rates are lower (+) stock should rebound

May 9, 2019

Key Takeaway

We spoke with management and we feel we have a very clear picture on the concept of the study...

- (1) In dialysis, Roxa showed a numerically lower cardiac event rate versus Epo (e.g. hazard ratio (HR) below 1.0 for dialysis). It was also statistically superior for incident dialysis.
- (2) The company feels very confident about Roxa's numerically lower event rate profile. In Europe, there was statistical non-inferiority for MACE+. In the US, the FDA analysis is based on the totality of data around MACE and because of that there is no statistical agreement on upper and lower bounds. As such, they cannot say whether it was "statistically non-inferior" on MACE for the FDA (i.e. there was no statistical definition). However, we just explained that the event rates are numerically lower with the hazard ratio (HR) of <1.0, and that is satisfying.
- (3) In non-dialysis, it is based on a time-to-event analysis which we believe (based on our conversations) is clearly numerically better for Roxa. The totality of MACE events is complicated because the control arm (placebo) quickly goes to dialysis and placebo patients drops off the study. Therefore the totality of MACE events is not relevant for analysis there because they are on Roxa for much longer versus placebo.

Bottom line, there is a lot of confusion on the data in the press release and the conference call, since it is a very complex dataset. Overall, we strongly believe that partners will file the drug in the US and Europe, which then triggers most of the \$192M of milestones anticipated in 2019, There is confusion in the market currently, but this should become clear as more investors realize the data is positive and Roxa's risk/benefit is favorable, so we see the stock rebounding and moving back up over time.

Estimate Change	
RATING	BUY
PRICE	\$45.67^
MARKET CAP	\$3.9B
PRICE TARGET (PT)	\$75.00
UPSIDE SCENARIO PT	\$150.00
DOWNSIDE SCENARIO PT	\$25.00

^Prior trading day's closing price unless otherwise noted.

FY Dec	2017A	2018A	2019E	2020E
EPS (\$)	(1.72)	(1.03)	1 (0.76)	↓ 0.30
Previous			(0.86)	0.38

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Please see analyst certifications, important disclosure information, and information regarding the status of non-US analysts on pages 5 to 10 of this report.

Jefferies

EQUITY RESEARCH FibroGen Inc (FGEN)

The Long View

Scenarios

Base Case

- Our \$75 PT is based on a SOTP:
- (1) roxadustat penetrating the anemia mkt and achieving \$3-4B+ peak WW sales (65-75% probability);
- (2) FG-3019 developed for IPF becoming a \$1.5B+ WW drug (40-50% probability);
- (3) Modest probability-adjusted credit to FG-3019's potential opportunity in other indications such as pancreatic cancer;
- (4) value from China economics for roxadustat if it was spunout (\$200-400M sales, 1-2x multiple)

Upside Scenario

- Our upside scenario of \$150 is based on a SOTP:
- (1) 90%+ probability of success for roxadustat approval and achieving \$5-6B+ peak WW sales (higher peak sales assumes roxadustat shows superiority)
- (2) 65-75% probability of success for FG-3019 for IPF and pancreatic cancer

Downside Scenario

- Our downside scenario of \$25 is based on a SOTP:
- (1) Low probability (0-10%) that roxadustat enters the market, taking into consideration the risk in running long, large Phase III trials as well as the high bar on safety
- (2) Some value ascribed to the IPF program
- (3) Remaining value in cash

Investment Thesis / Where We Differ

- We think FGEN is more de-risked at this point than the Street appreciates:
- (1) Roxadustat clearly shows strong efficacy from Phase II and Phase III studies, (2) China and Japan reported out positive initial positive Phase III results recently in 2017-18, (3) China approved Roxa in Dec 2018, (4) safety has been tested in 9,000+ patients through Phase III with no issues by DSMB (latest analysis conducted in Aug 2018).
- We also believe partners AZN and Astellas did significant diligence on pre-clinical toxicity and carcinogenicity models to de-risk safety.

Catalysts

- Begin Phase III studies for FG-3019 in IPF and pancreatic cancer in Q2
- Submit roxadustat NDA for regulatory approval in the USA in Sep/Oct and the EU in 2019
- Estimated approval of roxadustat in China in Mid-2019 (NDD)
- Secure China reimbursement for roxadustat in 2019-20

Long Term Analysis

LT Earnings CAGR	N/A
Organic Revenue Growth	N/A
Acquisition Contribution	N/A
Operating Margin Expansion	N/A



EQUITY RESEARCH FibroGen Inc (FGEN)

Financial Summary and Market Data

Financial Summary						
Long-Term Debt (MM)	\$1.4					
Cash & ST Invest. (MM)	\$712.7					

Market Data						
52-Week Range:	\$68.55 - \$37.27					
Total Entprs. Value	\$3.2B					
Avg. Daily Value MM (\$)	29.82					
Float (%)	89.0%					

Estimates and Valuation

	Estimates											
	Prev.	2017A Prev.		2018A	2018A Prev.		Prev.	2020E				
Rev. (MM)		128.2		213.0		192.5		345.0				
Consensus EPS		-		-		(1.27)		1.01				
EPS												
Q1		(0.48)		(0.50)	(0.79)	↑ (0.53)A		-				
Q2		(0.48)		(0.28)	(0.42)	◆ (0.54)		-				
Q3		(0.50)		(0.50)	0.18	• 0.16		-				
Q4		(0.27)		0.23	0.17	• 0.15		-				
FY Dec		(1.72)		(1.03)	(0.86)	1 (0.76)	0.38	• 0.30				
				Valuation								
		2017A		2018A		2019E		2020E				
P/Rev		30.5x		18.4x		20.3x		11.3x				

Jefferies

EQUITY RESEARCHFibroGen Inc (FGEN)

Exhibit 1 - FGEN Income Statement

(\$ in millions, except per share)	FY16	1Q17	2Q17	3Q17	4Q17	FY17	1Q18	2Q18	3Q18	4Q18	FY18	1Q19	2Q19E	3Q19E	4Q19E	FY19E	FY20E
Fiscal Year Ends December		Mar-17	Jun-17	Sep-17	Dec-17		Mar-18	Jun-18	Sep-18	Dec-18		Mar-19	Jun-19	Sep-19	Dec-19		
Revenues:																	
Roxadustat Sales (China)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	50.0
Roxadustat Royalties (US, ROW ex-China)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	45.0
FG-3019 Sales	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
License and milestone (old reporting)	137.4	-	21.4	20.0	35.1	76.5	-	-	-	-	-	-	-	-	-	-	-
License revenue	-	-	-	-	-	-	-	14.3	-	7.9	22.3	-	-	-	-	-	-
Collaboration services, milestones, other	42.2	29.4	7.6	7.3	7.4	51.7	31.9	29.6	29.0	100.1	190.7	23.9	18.6	75.0	75.0	192.5	250.0
Total Revenue	179.6	29.4	29.0	27.3	42.5	128.2	31.9	44.0	29.0	108.1	213.0	23.9	18.6	75.0	75.0	192.5	345.0
Costs and expenses:																	
Cost of product sales											-					-	7.6
Research and development	187.2	46.7	47.0	50.3	52.5	196.5	57.0	52.1	56.4	70.3	235.8	50.5	45.0	40.0	40.0	175.5	210.0
Selling, general and administrative	46.0	11.5	13.4	13.0	13.9	51.8	15.6	15.1	15.4	17.9	63.8	22.2	23.0	23.5	24.0	92.7	111.3
Total operating costs and expenses	233.2	58.3	60.4	63.3	66.3	248.3	72.5	67.2	71.8	88.1	299.7	72.7	68.0	63.5	64.0	268.2	328.9
Income (loss) from operations	(53.7)	(28.8)	(31.4)	(36.0)	(23.8)	(120.1)	(40.6)	(23.2)	(42.8)	19.9	(86.7)	(48.8)	(49.4)	11.5	11.0	(75.7)	16.1
Total interest and other, net	(8.1)	(1.7)	(1.7)	(1.7)	1.8	(3.3)	(0.7)	(0.1)	0.3	1.0	0.6	3.4	2.9	2.7	2.7	11.7	11.7
Income (loss) before income taxes	(61.8)	(30.6)	(33.1)	(37.7)	(22.0)	(123.3)	(41.3)	(23.3)	(42.4)	21.0	(86.1)	(45.4)	(46.5)	14.2	13.7	(64.0)	27.9
Benefit from income tax (provision)	0.1	(0.1)	(0.0)	(0.1)	(0.2)	(0.3)	(0.1)	(0.1)	(0.1)	(0.0)	(0.3)	(0.0)	(0.0)	(0.0)	(0.0)	(0.1)	(0.1)
Net income (loss)	(61.7)	(30.6)	(33.2)	(37.7)	(22.1)	(123.7)	(41.4)	(23.4)	(42.6)	21.0	(86.4)	(45.5)	(46.5)	14.2	13.7	(64.1)	27.8
EPS (basic)	(\$0.98)	(\$0.48)	(\$0.48)	(\$0.50)	(\$0.27)	(\$1.72)	(\$0.50)	(\$0.28)	(\$0.50)	\$0.25	(\$1.03)	(\$0.53)	(\$0.54)	\$0.16	\$0.15	(\$0.76)	\$0.30
EPS (diluted)	(\$0.98)	(\$0.48)	(\$0.48)	(\$0.50)	(\$0.27)	(\$1.72)	(\$0.50)	(\$0.28)	(\$0.50)	\$0.23	(\$1.03)	(\$0.53)	(\$0.54)	\$0.16	\$0.15	(\$0.76)	\$0.30
Basic	62.7	64.0	69.6	75.9	82.2	72.9	82.9	83.8	84.5	85.1	84.1	85.7	86.3	88.0	89.8	87.5	91.6
Diluted	64.4	64.0	69.6	75.9	82.2	72.9	82.9	83.8	84.5	91.3	85.6	85.7	86.3	88.0	89.8	87.5	91.6

Source: Jefferies estimates, Company reports



EQUITY RESEARCH FibroGen Inc (FGEN)

Company Description

FibroGen

FibroGen is a San Francisco-based biopharmaceutical company focused on the discovery, development and commercialization of novel therapeutics to treat anemia, fibrosis and cancer. The company's lead anemia product candidate roxadustat is an oral small molecule inhibitor of HIF-PH, partnered with AstraZeneca and Astellas around the world. Its lead IPF drug candidate FG-3019 is a monoclonal antibody that is also in development for pancreatic cancer and liver fibrosis and DMD.

Company Valuation/Risks

FibroGen

Our PT is based on a probability-adjusted DCF (WACC 8%; TG -10%) for Roxa and FG-3019. Risks include safety and efficacy, and reimbursement/competition.

Analyst Certification:

I, Michael J. Yee, certify that all of the views expressed in this research report accurately reflect my personal views about the subject security(ies) and subject company(ies). I also certify that no part of my compensation was, is, or will be, directly or indirectly, related to the specific recommendations or views expressed in this research report.

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Investment Recommendation Record

(Article 3(1)e and Article 7 of MAR)

Recommendation Published May 9, 2019, 20:56 ET.
Recommendation Distributed May 9, 2019, 20:56 ET.

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Underperform - Describes securities that we expect to provide a total return (price appreciation plus yield) of minus 10% or less within a 12-month period.

The expected total return (price appreciation plus yield) for Buy rated securities with an average security price consistently below \$10 is 20% or more within a 12-month period as these companies are typically more volatile than the overall stock market. For Hold rated securities with an average security price consistently below \$10, the expected total return (price appreciation plus yield) is plus or minus 20% within a 12-month period. For Underperform rated securities with an average security price consistently below \$10, the expected total return (price appreciation plus yield) is minus 20% or less within a 12-month period.

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I: Initiating Coverage

D: Dropped Coverage

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H: Hold

UP: Underperform

Distribution of Ratings

Distribution of Ratings											
IB Serv./Past12 Mos. JIL Mkt Serv./Past12 Mos.											
	Count	Percent	Count	Percent	Count	Percent					
BUY	1154	54.31%	94	8.15%	16	1.39%					
HOLD	824	38.78%	9	1.09%	1	0.12%					
UNDERPERFORM	147	6.92%	1	0.68%	0	0.00%					



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EXHIBIT L

UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form	10-Q
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(Mark (One)
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☑ QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the quarterly period ended March 31, 2019

OR

TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES
EXCHANGE ACT OF 1934

For the transition period from ______ to _____ Commission file number: 001-36740

FIBROGEN, INC.

(Exact name of registrant as specified in its charter)

Delaware

(State or Other Jurisdiction of Incorporation or Organization)

77-0357827 (I.R.S. Employer Identification No.)

409 Illinois Street
San Francisco, CA
(Address of Principal Executive Offices)

94158 (Zip Code)

(415) 978-1200 Registrant's telephone number, including area code:

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes \square No \square

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (\S 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes \square No \square

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act:

 Large accelerated filer
 ✓
 Accelerated filer
 □

 Non-accelerated filer
 □
 Smaller reporting company
 □

 Emerging growth company
 □

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. \Box

Indicate by check mark whether the registrant is a shell company (as defined in Exchange Act Rule 12b-2). Yes □ No ☑

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol	Name of each exchange on which					
		registered					
Common Stock, \$0.01 par value	FGEN	The Nasdaq Global Select Market					

The number of shares of common stock outstanding as of April 30, 2019 was 86,221,978.

11/4/21, 2:41 PM Case 3:21-cv-02623-EMC Document **ha**010**Eiberb**11/11/4/22 Page 474 of 526 **FIBROGEN, INC.**

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ITEM 2. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS.

You should read the following discussion and analysis of our financial condition and results of operations in conjunction with the condensed consolidated financial statements and the notes thereto included elsewhere in this Quarterly Report on Form 10-Q, and in our Securities and Exchange Commission ("SEC") filings, including our Annual Report on Form 10-K for the year ended December 31, 2018 filed with the SEC on February 27, 2019.

FORWARD-LOOKING STATEMENTS

The following discussion and information contained elsewhere in this Quarterly Report on Form 10-Q contain "forward-looking" statements" within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended ("Exchange Act"), Section 27A of the Securities Act of 1933, as amended ("Securities Act") and within the meaning of the Private Securities Litigation Reform Act of 1995. These statements are often identified by the use of words such as "may," "will," "expect," "believe," "anticipate," "intend," "could," "should," "estimate," or "continue," and similar expressions or variations. Such forward-looking statements are subject to risks, uncertainties and other factors that could cause actual results and the timing of certain events to differ materially from future results expressed or implied by such forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in the section titled "Risk Factors," set forth in Part II, Item 1A of this Quarterly Report on Form 10-Q. The forward-looking statements in this Quarterly Report on Form 10-Q represent our views as of the date of this Quarterly Report on Form 10-Q. We anticipate that subsequent events and developments will cause our views to change. New risks emerge from time to time, and it is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. In light of these risks, uncertainties, and assumptions, the forward-looking events and circumstances discussed in this Quarterly Report on Form 10-Q may not occur, and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements. While we may elect to update these forward-looking statements at some point in the future, we have no current intention of doing so except to the extent required by applicable law. You should, therefore, not rely on these forward-looking statements as representing our views as of any date subsequent to the date of this Quarterly Report on Form 10-O and are cautioned not to place undue reliance on such forward-looking statements.

BUSINESS OVERVIEW

We were incorporated in 1993 in Delaware and are a leading biopharmaceutical company discovering and developing a pipeline of first-in-class therapeutics. We have applied our pioneering expertise in hypoxia-inducible factor ("HIF") and connective tissue growth factor ("CTGF") biology to develop innovative medicines for the treatment of anemia, fibrotic disease, and cancer. Roxadustat (FG-4592), our most advanced product candidate, is an oral small molecule inhibitor of HIF prolyl hydroxylase ("HIF-PH") activity. Roxadustat has received approval of its New Drug Application ("NDA") in anemia associated with chronic kidney disease ("CKD") in dialysis-dependent patients from the National Medical Products Administration ("NMPA") of the People's Republic of China ("China"). In conjunction with our collaboration partners, AstraZeneca AB ("AstraZeneca") and Astellas Pharma Inc. ("Astellas"), we have completed the Phase 3 trials of roxadustat intended to support our NDA in the United States ("U.S.") and Marketing Authorization Application ("MAA") in the European Union ("EU") for the treatment of anemia in CKD. We and our partners are in the process of preparing an NDA for submission to the U.S. Food and Drug Administration ("FDA") and an MAA for submission to the European Medicines Agency ("EMA") this year. Both the U.S. NDA and European MAA for roxadustat are expected to cover anemia associated with dialysis-dependent CKD and non-dialysis-dependent CKD. In Japan, our partner Astellas has filed an NDA for roxadustat for the treatment of anemia in dialysis patients with the Pharmaceuticals and Medical Devices Agency ("PMDA"). We are also in Phase 3 clinical development for the treatment of anemia associated with myelodysplastic syndromes ("MDS"). Pamrevlumab, a human monoclonal antibody that inhibits the activity of CTGF, is advancing towards Phase 3 clinical development for the treatment of idiopathic pulmonary fibrosis ("IPF") and pancreatic cancer, and is currently in a Phase 2 trial for Duchenne muscular dystrophy ("DMD").

Financial Highlights

	Three Months Ended March 31,						
		2019	2018				
	(in thousands, except for per share data)						
Result of Operations							
Revenue	\$	23,863	\$	31,925			
Operating expenses	\$	72,706	\$	72,524			
Net loss	\$	(45,411)	\$	(41,396)			
Net loss per share - basic and diluted	\$	(0.53)	\$	(0.50)			
		March 31, 2019		December 31, 2018			
	(in thousands)			ds)			
Balance Sheet							
Cash and cash equivalents	\$	81,673	\$	89,258			
Short-term and long-term investments	\$	615,929	\$	587,964			
Accounts receivable	\$	6,023	\$	63,684			

Our revenue for the three months ended March 31, 2019 decreased compared to the same period a year ago primarily due to a decrease in co-development billings related to the development of roxadustat as a result of the substantial completion of Phase 3 trials for roxadustat.

Operating expenses for the three months ended March 31, 2019 remained relatively flat compared to the same period a year ago primarily due to \$5.6 million higher stock-based compensation related to the cumulative impact of stock option grant activities, \$2.6 million amortization of finance lease right-of-use ("ROU") assets related to the adoption of lease accounting guidance under Accounting Standards Codification ("ASC") 842 - *Leases* ("ASC 842"), \$2.1 million higher outside service expenses related to copromotional activities and scientific contract expenses, and \$1.2 million higher depreciation expenses due to the change in estimated useful life for our leasehold improvements as a result of the adoption of ASC 842. The increases were offset by \$8.3 million lower clinical trial activities related to roxadustat and \$3.6 million lower drug development expenses associated with drug substance manufacturing activities related to pamrevlumab and roxadustat.

During the three months ended March 31, 2019, we had a net loss of \$45.4 million, or net loss per basic and diluted share of \$0.53, as compared to a net loss of \$41.4 million for the same period a year ago, due to a decrease in revenue.

Cash and cash equivalents, investments and accounts receivable totaled \$703.6 million at March 31, 2019, a decrease of \$37.3 million from December 31, 2018, primarily due to the cash used in operations.

Programs

Roxadustat for the Treatment of Anemia in Chronic Kidney Disease

Roxadustat is our most advanced product candidate, an oral small molecule inhibitor of HIF-PH activity that acts by stimulating the body's natural pathway of erythropoiesis, or red blood cell production. We received our first NDA approval in China for roxadustat for the treatment of anemia caused by CKD in dialysis patients in December of 2018.

In conjunction with our collaboration partners, AstraZeneca and Astellas, we also reported top line efficacy data from the Phase 3 trials of roxadustat intended to support our NDA in the U.S. and MAA in the EU for the treatment of anemia in CKD.

We have completed initial analyses of the adjudicated safety data for the pooled dialysis-dependent patient population, the incident dialysis subpopulation (of the overall dialysis population), as well as for the pooled non-dialysis patient population from our, and our partners', Phase 3 CKD-anemia trials.

With the understanding that regulatory authorities will need to review the data and conduct their own analyses and evaluation of the overall benefit-risk profile of roxadustat, our NDA submission package to the FDA will be based on the totality of evidence of efficacy and safety. We have had extensive discussions with the FDA on the specific statistical standards for the various analyses and endpoints and we are planning to seek further input from the FDA on the content and format of our planned NDA submission package in an upcoming pre-NDA meeting to facilitate the FDA's review of the package. One of the key safety endpoints to be evaluated is time to first Major Adverse Cardiac Event ("MACE"), a composite endpoint of all-cause mortality, stroke and myocardial infarction.

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In Europe, the primary safety endpoint is the time to first MACE+ event ("MACE+") which, in addition to the components in MACE, also includes hospitalization due to heart failure or unstable angina.

Pooled MACE/MACE+ in Dialysis

The pooled dialysis population consists of approximately 4,000 patients. In the MACE+ analyses, the upper bound of the 95% confidence interval of the hazard ratios were below the pre-specified non-inferiority margin for Europe.

For the U.S., where the focus will be on MACE, based on the collective results of the various MACE analyses, we believe there is no clinically meaningful difference in MACE risks between roxadustat and epoetin alfa.

Pooled MACE/MACE+ in Incident Dialysis

The roxadustat global Phase 3 program enrolled over 1,500 incident dialysis patients, a subgroup of dialysis patients that have newly initiated dialysis. We believe incident dialysis offers a better setting for comparing roxadustat to erythropoiesis stimulating agents ("ESAs") as the stable dialysis population contains the twin biases of patients who have already survived the incident period, which is associated with increased mortality rates, and patients who have already responded to stable doses of ESA after dose-titration.

In MACE+, roxadustat demonstrated superiority to epoetin alfa in this incident dialysis subpopulation.

In the MACE analysis of this same subgroup, there was a trend toward reduced risk of MACE for patients on roxadustat, compared to epoetin alfa.

Pooled MACE/MACE+ in Non-Dialysis Population

The non-dialysis pool consists of approximately 4,300 patients. In the MACE+ analyses, non-inferiority was demonstrated for roxadustat compared to placebo based on the upper bound of the 95% confidence interval being below the pre-specified non-inferiority margin for Europe.

For the U.S., where the focus will be on MACE, based on the collective results of the various MACE analyses, we believe there is no clinically meaningful difference in MACE safety between roxadustat and placebo in this same non-dialysis population.

Of note, we have conducted multiple MACE and MACE+ intent-to-treat analyses in non-dialysis patients followed for long-term safety results. These are among several statistical methods we will discuss with the FDA at a pre-NDA meeting to account for the substantially higher drop-out rates in the placebo arm. We had previously discussed, and the FDA acknowledged, the likelihood of this higher placebo patient drop-out rate that we observed in these non-dialysis studies. In these analyses, roxadustat was comparable to placebo, based on a commonly applied non-inferiority margin of 1.3.

Estimated Glomerular Filtration Rate Attenuation in Non-Dialysis

We believe there could be significant clinical benefit of roxadustat treatment in the non-dialysis CKD patient population if we are able to show attenuation of renal disease progression. The estimated glomerular filtration rate ("eGFR") is a measure of the filtration function of kidney and renal disease progression. In the preliminary analysis of our pooled Phase 3 non-dialysis studies (ANDES, ALPS, and OLYMPUS) of patients with eGFR 15 or higher (CKD stages 3 and 4), the one-year decline in eGFR in roxadustat treated patients was shown to be significantly less than that in placebo treated patients, with a treatment difference of 1.62 mL/min/1.73m2 at 12 months from the baseline (p<0.0001), or a reduction by 38% in eGFR decline in the roxadustat arm relative to the placebo arm.

Improvements in Quality of Life Measures in Non-Dialysis

We have also observed improvements in quality of life. In the pooled analysis from the three non-dialysis studies, we observed statistically significant improvements from baseline to Week 12 in quality of life endpoints, including SF-36 Vitality subscale (p=0.0002), SF-36 Physical Functioning subscale (p=0.0369), FACT-AN Anemia subscale (p=0.0012), FACT-AN Total score (p=0.0056), and EQ-5D-SL VAS score (p=0.0005) when comparing roxadustat to placebo in CKD patients not on dialysis.

Efficacy Regardless of Inflammation Status

Roxadustat has shown efficacy regardless of inflammation status as the mean achieved hemoglobin levels and roxadustat dose requirements were not impacted by patients' baseline CRP levels in multiple Phase 3 studies, including in the U.S. based SIERRAS study, which we believe is reflective of U.S. dialysis practice under current ESA labeling restrictions. In SIERRAS, roxadustat dose requirements remained stable over time for patients with both high and low baseline CRP levels, while epoetin alfa dose requirements for all patients in the comparator arm increased by 57% over 52 weeks.

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Encouraged by these results, we and our partners are preparing an NDA for submission to the FDA in September or October of 2019 and an MAA for submission to the EMA thereafter.

In China, roxadustat received NDA approval in December 2018 from the NMPA for the treatment of anemia caused by CKD in dialysis patients. Clinical site inspections for our Phase 3 non-dialysis study have now been completed by the China Food and Drug Inspection division of the NMPA and we expect the population of non-dialysis CKD patients to be added to the CKD anemia indication in the roxadustat label in mid-2019. The NMPA has recently approved us to manufacture roxadustat from our commercial API manufacturing facility in Cangzhou and we are planning commercial launch of roxadustat in China in the third quarter of 2019.

In Japan, Astellas submitted an NDA for the treatment of anemia in CKD patients on dialysis in September 2018, which is currently under review by the PMDA. We expect an approval decision on the Japan dialysis NDA in the second half of 2019.

Roxadustat for the Treatment of Anemia in Myelodysplastic Syndromes

In addition to anemia in CKD, roxadustat is in Phase 3 clinical development for the treatment of anemia associated with MDS and we plan to initiate a Phase 2 clinical trial of roxadustat in the U.S. in chemotherapy induced anemia in 2019.

We have completed enrollment of the 24-patient open-label, lead-in portion of our multi-center Phase 3 global study in transfusion-dependent, lower risk MDS patients. Encouraged by positive interim results, we have begun enrolling the 160-patient double-blind, placebo-controlled portion of the study, in which subjects will be randomized 3:2 to receive roxadustat or placebo three-times-weekly for 28 weeks, with safety extension to one year. The primary endpoint is the proportion of patients who achieve transfusion independence.

In China, we continue to enroll the open-label portion of our Phase 2/3 clinical trial to evaluate the safety and efficacy of roxadustat in non-transfusion dependent, lower risk MDS patients with anemia. After the open-label portion we expect to begin the 135-patient double-blind, placebo-controlled Phase 3 portion of the study, in which subjects will be randomized 2:1 to receive roxadustat or placebo three-times weekly for 26 weeks. The primary endpoint for this study is percentage of patients achieving a hemoglobin response.

Pamrevlumab (FG-3019) – Monoclonal Antibody Against Connective Tissue Growth Factor (CTGF)

Pamrevlumab is our human monoclonal antibody that inhibits the activity of CTGF, a central mediator and critical common element in the progression of fibrotic and fibro-proliferative diseases. We are advancing pamrevlumab toward Phase 3 clinical development for the treatment of IPF and locally advanced unresectable pancreatic cancer, and recently received 1-year data from our ongoing Phase 2 trial for DMD.

In the U.S., pamrevlumab has now received orphan drug designation for DMD in addition to IPF and pancreatic cancer, and Fast Track designation for the treatment of both IPF patients and patients with locally advanced unresectable pancreatic cancer from the FDA.

Locally Advanced Unresectable Pancreatic Cancer

We plan to begin enrolling a double-blind placebo controlled Phase 3 trial of pamrevlumab as a neoadjuvant therapy for locally advanced unresectable pancreatic cancer in the second quarter of 2019. We intend to enroll approximately 260 patients, randomized 1:1 to receive either pamrevlumab, in combination with gemcitabine and nab-paclitaxel, or chemotherapy with placebo.

Idiopathic Pulmonary Fibrosis

We also plan to begin enrolling our double-blind, placebo-controlled Phase 3 trial of pamrevlumab in approximately 500 IPF patients in the second quarter of 2019. This study is powered to meet the FDA requirement of a highly statistically-significant result in the primary efficacy endpoint of change from baseline in forced vital capacity ("FVC").

Duchenne Muscular Dystrophy

In DMD, all 21 non-ambulatory patients from our fully enrolled Phase 2 open-label single-arm trial have completed one year of treatment with pamrevlumab. While it is difficult to make comparisons between our trial and previously published data due to, among other things, differences in subject numbers, baseline characteristics, inclusion/exclusion criteria, treatment protocols, and analysis methods, we performed a one-year administrative analysis comparing our Phase 2 data to recent published natural disease history studies of DMD patients.

In pulmonary function tests, the results from our study indicate a potential reduction in the rate of decline in FVC percent predicted from baseline for our pamrevlumab-treated patients when compared to historical data of non-treated DMD patients published in 2016 by Meier and in 2019 by Ricotti.

In a cardiac function, measured by mean change of left ventricular ejection fraction ("LVEF"), the data showed an *increase* in cardiac function from baseline for our pamrevlumab-treated patients, while the published data by McDonald in 2018 showed a mean LVEF decline of approximately 1% from baseline in one year.

In muscle function tests, some of the results of this Phase 2 study showed the mean change from baseline for our pamrevlumab-treated patients was smaller than the published data of non-treated DMD patients from Ricotti in 2019.

Based on our administrative analysis and advice we received from expert advisors, we are planning to share these results with the FDA to refine our clinical development plan for DMD.

Collaboration Partnerships for Roxadustat

Our current and future research, development, manufacturing and commercialization efforts with respect to roxadustat and our other product candidates currently in development depend on funds from our collaboration agreements with Astellas and AstraZeneca as described below.

Astellas

In June 2005, we entered into a collaboration agreement with Astellas for the development and commercialization (but not manufacture) of roxadustat for the treatment of anemia in Japan ("Japan Agreement"). In April 2006, we entered into the Europe Agreement with Astellas for roxadustat for the treatment of anemia in Europe, the Commonwealth of Independent States, the Middle East, and South Africa. Under these agreements, we provide Astellas the right to develop and commercialize roxadustat for anemia indications in these territories.

We share responsibility with Astellas for clinical development activities required for the U.S. and the EU regulatory approval of roxadustat, and share equally those development costs under the agreed development plan for such activities. Astellas will be responsible for clinical development activities and all associated costs required for regulatory approval in all other countries in the Astellas territories. Astellas will own and have responsibility for regulatory filings in its territories. We are responsible, either directly or through our contract manufacturers, for the manufacture and supply of all quantities of roxadustat to be used in development and commercialization under the agreements.

The Astellas agreements will continue in effect until terminated. Either party may terminate the agreements for certain material breaches by the other party. In addition, Astellas will have the right to terminate the agreements for certain specified technical product failures, upon generic sales reaching a particular threshold, upon certain regulatory actions, or upon our entering into a settlement admitting the invalidity or unenforceability of our licensed patents. Astellas may also terminate the agreements for convenience upon advance written notice to us. In the event of any termination of the agreements, Astellas will transfer and assign to us the regulatory filings for roxadustat and will assign or license to us the relevant trademarks used with the products in the Astellas territories. Under certain terminations, Astellas is also obligated to pay us a termination fee.

Consideration under these agreements includes a total of \$360.1 million in upfront and non-contingent payments, and milestone payments totaling \$557.5 million, of which \$542.5 million are development and regulatory milestones and \$15.0 million are commercial-based milestones. Total consideration, excluding development cost reimbursement and product sales-related payments, could reach \$917.6 million. The aggregate amount of such consideration received through March 31, 2019 totals \$487.6 million. Additionally, under these agreements, Astellas pays 100% of the commercialization costs in its territories. Astellas will pay us a transfer price, based on net sales, in the low 20% range for our manufacture and delivery of roxadustat.

In addition, as of March 31, 2019, Astellas had separate investments of \$80.5 million in the equity of FibroGen, Inc.

AstraZeneca

In July 2013, we entered into the U.S./RoW Agreement, a collaboration agreement with AstraZeneca for roxadustat for the treatment of anemia in the U.S. and all territories not previously licensed to Astellas, except China. In July 2013, through our China subsidiary and related affiliates, we entered into the China Agreement, a collaboration agreement with AstraZeneca for roxadustat for the treatment of anemia in China. Under these agreements we provide AstraZeneca the right to develop and commercialize roxadustat for anemia in these territories. We share responsibility with AstraZeneca for clinical development activities required for U.S. regulatory approval of roxadustat.

In 2015, we reached the \$116.5 million cap on our initial funding obligations (during which time we shared 50% of the joint initial development costs), therefore all development and commercialization costs for roxadustat for the treatment of anemia in CKD in the U.S., Europe, Japan and all other markets outside of China have been paid by Astellas and AstraZeneca since reaching the cap.

In China, FibroGen (China) Medical Technology Development Co., Ltd. ("FibroGen Beijing") will conduct the development work for CKD anemia, will hold all of the regulatory licenses issued by China regulatory authorities, and will be primarily responsible for regulatory, clinical and manufacturing. China development costs are shared 50/50. AstraZeneca is also responsible for 100% of development expenses in all other licensed territories outside of China. We are responsible, through our contract manufacturers, for the manufacture and supply of all quantities of roxadustat to be used in development and commercialization under the AstraZeneca agreements.

Under the AstraZeneca agreements, we will receive upfront and subsequent non-contingent payments totaling \$402.2 million. Potential milestone payments under the agreements total \$1.2 billion, of which \$571.0 million are development and regulatory milestones and \$652.5 million are commercial-based milestones. Total consideration under the agreements, excluding development cost reimbursement, transfer price payments, royalties and profit share, could reach \$1.6 billion. The aggregate amount of such consideration received through March 31, 2019 totals \$444.2 million.

Under the U.S./RoW Agreement, AstraZeneca will pay for all commercialization costs in the U.S. and RoW and AstraZeneca will be responsible for the U.S. commercialization of roxadustat, with FibroGen undertaking specified promotional activities in the end-stage renal disease segment in the U.S. In addition, we will receive a transfer price for delivery of commercial product based on a percentage of net sales in the low- to mid-single digit range and AstraZeneca will pay us a tiered royalty on net sales of roxadustat in the low 20% range.

Under the China Agreement, which is conducted through FibroGen China Anemia Holdings, Ltd. ("FibroGen China"), the commercial collaboration is structured as a 50/50 profit share. AstraZeneca will conduct commercialization activities in China as well as serve as the master distributor for roxadustat and fund roxadustat launch costs in China until FibroGen Beijing has achieved profitability. At that time, AstraZeneca will recoup 50% of their historical launch costs out of initial roxadustat profits in China.

Payments under these agreements include over \$500.0 million in upfront, non-contingent and other payments received or expected to be received prior to the first U.S. approval, excluding development expense reimbursement.

AstraZeneca may terminate the U.S./RoW Agreement upon specified events, including our bankruptcy or insolvency, our uncured material breach, technical product failure, or upon 180 days prior written notice at will. If AstraZeneca terminates the U.S./RoW Agreement at will, in addition to any unpaid non-contingent payments, it will be responsible for paying for a substantial portion of the post-termination development costs under the agreed development plan until regulatory approval.

AstraZeneca may terminate the China Agreement upon specified events, including our bankruptcy or insolvency, our uncured material breach, technical product failure, or upon advance prior written notice at will. If AstraZeneca terminates our China Agreement at will, it will be responsible for paying for transition costs as well as make a specified payment to FibroGen China.

In the event of any termination of the agreements, but subject to modification upon termination for technical product failure, AstraZeneca will transfer and assign to us any regulatory filings and approvals for roxadustat in the affected territories that they may hold under our agreements, grant us licenses and conduct certain transition activities.

Additional Information Related to Collaboration Agreements

Total cash consideration received through March 31, 2019 and potential cash consideration, other than development cost reimbursement, transfer price payments, royalties and profit share, pursuant to our existing collaboration agreements are as follows:

	Cash Received Through March 31, 2019		Additional Potential sh Payments thousands)	Total Potential Cash Payments	
Astellasrelated-party:		(III)	thousands)		
Japan Agreement	\$ 77,593	\$	95,000	\$	172,593
Europe Agreement	410,000		335,000		745,000
Total Astellas	 487,593		430,000		917,593
AstraZeneca:					
U.S. / RoW Agreement	389,000		860,000		1,249,000
China Agreement	55,200		321,500		376,700
Total AstraZeneca	 444,200		1,181,500		1,625,700
Total revenue	\$ 931,793	\$	1,611,500	\$	2,543,293

These collaboration agreements also provide for reimbursement of certain fully burdened research and development costs as well as direct out of pocket expenses.

RESULTS OF OPERATIONS

Revenue

	_Thi	Three Months Ended March 31,				Change				
	2019		2018				%			
	(dollars in thousands)									
Revenue:										
License revenue	\$	_	\$	_	\$	_	— %			
Development and other revenue		23,863		31,925		(8,062)	(25)%			
Total revenue	\$	23,863	\$	31,925	\$	(8,062)	(25)%			

Our revenue to date has been generated substantially from our collaboration agreements with Astellas and AstraZeneca.

Under our revenue recognition policy, license revenue includes amounts from upfront, non-refundable license payments and amounts allocated pursuant to the standalone selling price method from other consideration received during the periods. This revenue is generally recognized as deliverables are met and services are performed. We did not have any license revenue for the three months ended March 31, 2019 and 2018.

Development revenue include co-development and other development related services. Co-development services are recognized as revenue in the period in which they are billed to our partners, excluding China. For China co-development services, revenue is deferred until the end of the development period once all performance obligations have been satisfied. Other development related services are recognized as revenue over the non-contingent development period, ranging from 36 to 89 months, based on a proportional performance method. Other revenues consist of sales of research and development material and have been included with Development and other revenue in the condensed consolidated statements of operations, as they have not been material for any of the years presented.

PART II—OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

We are not currently a party to any material legal proceedings.

ITEM 1A. RISK FACTORS

Investing in our common stock involves a high degree of risk. You should carefully consider the risks described below in addition to the other information included or incorporated by reference in this Quarterly Report on Form 10-Q, including our condensed consolidated financial statements and the related notes and "Management's Discussion and Analysis of Financial Condition and Results of Operations," before deciding whether to invest in our common stock. The occurrence of any of the events or developments described below could harm our business, financial condition, results of operations and growth prospects. In such an event, the market price of our common stock could decline, and you may lose all or part of your investment. Although we have discussed all known material risks, the risks described below are not the only ones that we may face. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also impair our business operations.

We have marked with an asterisk (*) those risks described below that reflect substantive changes from the risks described under Part I, Item 1A "Risk Factors" included in our Annual Report on Form 10-K for the year ended December 31, 2018.

Risks Related to Our Financial Condition and History of Operating Losses

We have incurred significant losses since our inception and anticipate that we will continue to incur losses for the foreseeable future and may never achieve or sustain profitability. We may require additional financings in order to fund our operations.*

We are a clinical-stage biopharmaceutical company with two lead product candidates in clinical development, roxadustat in anemia in chronic kidney disease ("CKD") and myelodysplastic syndromes ("MDS"), and pamreylumab (FG-3019) in idiopathic pulmonary fibrosis ("IPF"), pancreatic cancer and Duchenne muscular dystrophy ("DMD"). Pharmaceutical product development is a highly risky undertaking. To date, we have focused our efforts and most of our resources on hypoxia-inducible factor ("HIF") and fibrosis biology research, as well as developing our lead product candidates. We are not profitable and, other than in 2006 and 2007 due to income received from our Astellas Pharma Inc. ("Astellas") collaboration, have incurred losses each year since our inception. We have not generated any revenue based on commercial drug product sales to date. We continue to incur significant research and development and other expenses related to our ongoing operations. Our net loss for the year ended December 31, 2018 was approximately \$86.4 million, and our net loss for the years ended December 31, 2017, and 2016, recast from amounts previously reported due to the adoption of the new revenue standards, were approximately \$120.9 million and \$58.1 million, respectively. As of March 31, 2019, we had an accumulated deficit of \$753.2 million. As of March 31, 2019, we had capital resources consisting of cash, cash equivalents and shortterm investments of \$565.4 million plus \$132.2 million of long-term investments classified as available for sale securities. Despite contractual development and cost coverage commitments from our collaboration partners, AstraZeneca AB ("AstraZeneca") and Astellas, and the potential to receive milestone and other payments from these partners, and despite our expectation to launch commercialization efforts in China for roxadustat for the treatment of anemia caused by CKD in dialysis patients, we anticipate we will continue to incur losses for the foreseeable future, and we anticipate these losses will increase as we continue our development of and seek regulatory approval for our product candidates and in our commercialization efforts. If we do not successfully develop and obtain regulatory approval for our existing or any future product candidates and effectively manufacture, market and sell any product candidates that are approved, we may never generate product sales, and even if we do generate product sales, we may never achieve or sustain profitability on a quarterly or annual basis. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our stockholders' equity and working capital. Our failure to become and remain profitable would depress the market price of our common stock and could impair our ability to raise capital, expand our business, diversify our product offerings or continue our operations.

We believe that we will continue to expend substantial resources for the foreseeable future as we continue late-stage clinical development of roxadustat, grow our operations in the People's Republic of China ("China"), expand our clinical development efforts on pamrevlumab, seek regulatory approval, prepare for the commercialization of our product candidates, and pursue additional indications. These expenditures will include costs associated with research and development, conducting preclinical trials and clinical trials, obtaining regulatory approvals in various jurisdictions, and manufacturing and supplying products and product candidates for ourselves and our partners. In particular, in our planned Phase 3 clinical trial program for roxadustat, which we believe will be the largest Phase 3 program ever conducted for an anemia product candidate, we are expecting to enroll more than 8,000 patients for our U.S. and European programs alone. We are conducting this Phase 3 program in conjunction with Astellas and AstraZeneca, and we are substantially dependent on Astellas and AstraZeneca for the funding of this large program. The outcome of any clinical trial and/or regulatory approval process is highly uncertain and we are unable to fully estimate the actual costs necessary to successfully complete the development and regulatory approval process for our compounds in development and any future product candidates. We believe that the net proceeds from our 2017 public offerings, our existing cash and cash equivalents, short-term and long-term investments and accounts receivable, and expected third party collaboration revenues will allow us to fund our operating plans through at least the next 12 months. Our operating plans or third party collaborations may change as a result of many factors, which are discussed in more detail below, and other factors that may not currently be known to us, and we therefore may need to seek additional funds sooner than planned, through offerings of public or private securities, debt financings or other sources, such as royalty monetization or other structured financings. Such financings may result in dilution to stockholders, imposition of debt covenants and repayment obligations, or other restrictions that may adversely affect our business. We may also seek additional capital due to favorable market conditions or strategic considerations even if we currently believe that we have sufficient funds for our current or future operating plans.

Our future funding requirements will depend on many factors, including, but not limited to:

- the rate of progress in the development of our product candidates;
- the costs of development efforts for our product candidates, such as pamrevlumab, that are not subject to reimbursement from our collaboration partners;
- the costs necessary to obtain regulatory approvals, if any, for our product candidates in the United States ("U.S."), China and other jurisdictions, and the costs of post-marketing studies that could be required by regulatory authorities in jurisdictions where approval is obtained;
- the continuation of our existing collaborations and entry into new collaborations;
- the time and unreimbursed costs necessary to commercialize products in territories in which our product candidates are approved for sale;
- the revenues from any future sales of our products as well as revenue earned from profit share, royalties and milestones;
- the level of reimbursement or third party payor pricing available to our products;
- the costs of establishing and maintaining manufacturing operations and obtaining third party commercial supplies of our products, if any, manufactured in accordance with regulatory requirements;
- the costs we incur in maintaining domestic and foreign operations, including operations in China;
- regulatory compliance costs:
- the costs of our commercialization efforts for roxadustat for the treatment of anemia caused by CKD in dialysis patients in China; and
- the costs we incur in the filing, prosecution, maintenance and defense of our extensive patent portfolio and other intellectual property rights.

Additional funds may not be available when we require them, or on terms that are acceptable to us. If adequate funds are not available to us on a timely basis, we may be required to delay, limit, reduce or terminate our research and development efforts or other operations or activities that may be necessary to commercialize our product candidates.

All of our recent revenue has been earned from collaboration partners for our product candidates under development.

Substantially all of our revenues recognized in recent years have been from our collaboration partners.

We will require substantial additional capital to achieve our development and commercialization goals, which for our lead product candidate, roxadustat, is currently contemplated to be provided under our existing third party collaborations with Astellas and AstraZeneca.

If either or both of these collaborations were to be terminated, we could require significant additional capital in order to proceed with development and commercialization of our product candidates, including with respect to our expected commercialization for roxadustat for the treatment of anemia caused by CKD in dialysis patients in China, or we may require additional partnering in order to help fund such development and commercialization. If adequate funds or partners are not available to us on a timely basis or on favorable terms, we may be required to delay, limit, reduce or terminate our research and development efforts or other operations.

If we are unable to continue to progress our development efforts and achieve milestones under our collaboration agreements, our revenues may decrease and our activities may fail to lead to commercial products.

Substantially all of our revenues to date have been, and a significant portion of our future revenues are expected to be, derived from our existing collaboration agreements. Revenues from research and development collaborations depend upon continuation of the collaborations, reimbursement of development costs, the achievement of milestones and royalties and profits from our product sales, if any, derived from future products developed from our research. If we are unable to successfully advance the development of our product candidates or achieve milestones, revenues under our collaboration agreements will be substantially less than expected.

Risks Related to the Development and Commercialization of Our Product Candidates

We are substantially dependent on the success of our lead product candidate, roxadustat, and our second compound in development, pamrevlumab.*

To date, we have invested a substantial portion of our efforts and financial resources in the research and development of roxadustat and pamrevlumab. While we have received approval of our New Drug Application ("NDA") for roxadustat in China for CKD anemia in dialysis patients, we will need to make substantial additional investments in both the development and commercialization of roxadustat worldwide and in various indications. Our near-term prospects, including maintaining our existing collaborations with Astellas and AstraZeneca, will depend heavily on successful development and commercialization of roxadustat, including obtaining regulatory approvals for the commercialization of roxadustat for anemia associated with CKD in the U.S., Europe, and Japan.

Our other lead product candidate, pamrevlumab, is currently in clinical development for IPF, pancreatic cancer and DMD. Pamrevlumab requires substantial further development and investment. We do not have a collaboration partner for support of this compound, and, while we have promising open-label safety data and potential signals of efficacy, we would need to complete larger and more extensive controlled clinical trials to validate the results to date in order to continue further development of this product candidate. In addition, although there are many potentially promising indications beyond IPF, pancreatic cancer and DMD, we are still exploring indications for which further development of, and investment for, pamrevlumab may be appropriate. Accordingly, the costs and time to complete development and related risks are currently unknown. Moreover, pamrevlumab is a monoclonal antibody, which may require experience and expertise that we may not currently possess as well as financial resources that are potentially greater than those required for our small molecule lead compound, roxadustat.

The clinical and commercial success of roxadustat and pamrevlumab will depend on a number of factors, many of which are beyond our control, and we may be unable to complete the development or commercialization of roxadustat or pamrevlumab.*

The clinical and commercial success of roxadustat and pamrevlumab will depend on a number of factors, including the following:

- the timely completion of data analyses from our Phase 3 clinical trials for roxadustat, which will depend substantially upon requirements for such trials imposed by the U.S. Food and Drug Administration ("FDA") and other regulatory agencies and bodies and the continued commitment and coordinated and timely performance by our third party collaboration partners, AstraZeneca and Astellas;
- the timely initiation and completion of our clinical trials for pamrevlumab, including in IPF, pancreatic cancer and DMD;
- our ability to demonstrate the safety and efficacy of our product candidates to the satisfaction of the relevant regulatory authorities;

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- the ultimate approval criteria (including non-inferiority margins and statistical analyses methods), indications, patient populations, and ultimate benefit-risk analysis used by regulatory authorities in their approval processes;
- whether we are required by the FDA or other regulatory authorities to conduct additional clinical trials, and the scope and nature of such clinical trials, prior to approval to market our products;
- the timely receipt of necessary marketing approvals from the FDA and foreign regulatory authorities, including pricing and reimbursement determinations;
- the ability to successfully commercialize our product candidates, if approved, for marketing and sale by the FDA or foreign regulatory authorities, whether alone or in collaboration with others;
- our ability and the ability of our third party manufacturing partners to manufacture quantities of our product candidates at quality levels necessary to meet regulatory requirements and at a scale sufficient to meet anticipated demand at a cost that allows us to achieve profitability;
- our success in educating health care providers and patients about the benefits, risks, administration and use of our product candidates, if approved;
- acceptance of our product candidates, if approved, as safe and effective by patients and the healthcare community;
- the success of efforts to enter into relationships with large dialysis organizations involving the administration of roxadustat to dialysis patients;
- the achievement and maintenance of compliance with all regulatory requirements applicable to our product candidates;
- the maintenance of an acceptable safety profile of our products following any approval;
- the availability, perceived advantages, relative cost, relative safety, and relative efficacy of alternative and competitive treatments;
- our ability to obtain and sustain an adequate level of pricing or reimbursement for our products by third party payors;
- our ability to enforce successfully our intellectual property rights for our product candidates and against the products of potential competitors; and
- our ability to avoid or succeed in third party patent interference or patent infringement claims.

Many of these factors are beyond our control. Accordingly, we cannot assure you that we will ever be able to achieve profitability through the sale of, or royalties from, our product candidates. If we or our collaboration partners are not successful in obtaining approval for and commercializing our product candidates, or are delayed in completing those efforts, our business and operations would be adversely affected.

If our commercialization efforts for roxadustat in China are unsuccessful, our business, financial condition and results of operations will be materially harmed.

We have invested and continue to invest a significant portion of our efforts and financial resources in the development, approval and now commercialization of roxadustat for the treatment of anemia caused by CKD in dialysis patients in China, as well as in other indications and other geographic regions. With the marketing authorization received from the National Medical Products Administration ("NMPA") of roxadustat for the treatment of anemia caused by CKD in dialysis patients in China, we plan to launch commercialization efforts in China in the third quarter of 2019 with our commercialization partner AstraZeneca.

Our success of commercialization of roxadustat in China will depend on numerous factors in China, including:

- our success in the marketing, sales, and distribution of the product along with our collaboration partner AstraZeneca;
- our success in negotiating a cost effective reimbursed price with the government in China;
- acceptance of roxadustat by state-owned and state-controlled hospitals, physicians, patients and the healthcare community;
- acceptance of pricing and placement of roxadustat on China's Medical Insurance Catalogs. Refer to "Business Government Regulation Regulation in China";
- successfully establishing and maintaining commercial manufacturing with third parties;

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- successfully manufacturing our drug substances and drug products through our subsidiary FibroGen (China) Medical Technology Development Co., Ltd. ("FibroGen Beijing");
- receiving market authorization for roxadustat for anemia caused by CKD in non-dialysis patients;
- our success in arranging for and passing the inspection of our clinical sites by the NMPA;
- whether AstraZeneca is able to recruit and retain adequate numbers of effective sales and marketing personnel for the sale of roxadustat;
- whether we can compete successfully as a new entrant in the treatment of anemia caused by CKD in dialysis patients in China; and
- whether we will maintain sufficient funding to cover the costs and expenses associated with creating and sustaining a capable sales and marketing organization and related commercial infrastructure.

Successful commercialization of roxadustat will require significant resources and time, and there is a risk that we may not successfully commercialize roxadustat. If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize roxadustat and generate revenues, which would deprive us from additional working capital and would materially harm our business. If we do not successfully commercialize roxadustat in China, our collaboration partners and third parties may also lose confidence in our ability to execute in commercialization efforts and become less likely to collaborate with us, and our business may be harmed.

As a Company, we have no commercialization experience, and the time and resources to develop such experience are significant. If we fail to achieve and sustain commercial success for roxadustat in China, either directly or with AstraZeneca, our business would be harmed.

Commercializing roxadustat in China with AstraZeneca will require us to establish commercialization systems, including but not limited to, medical affairs, sales, pharmacovigilance, supply-chain, and distribution capabilities to perform our portion of the collaborative efforts. These efforts will require resources and time. In particular, significant resources may be necessary to successfully market, sell and distribute roxadustat to patients with anemia caused by CKD in dialysis patients. If we, along with AstraZeneca, are not successful in setting our marketing, pricing and reimbursement strategy, facilitating adoption by hospitals in China, recruiting sales and marketing personnel or in building a sales and marketing infrastructure, we will have difficulty commercializing roxadustat, which would adversely affect our business and financial condition.

As we evolve from a company primarily involved in research and development to a company potentially involved in commercialization, we may encounter difficulties in managing our growth and expanding our operations successfully.

If we are successful in advancing roxadustat and our other product candidates through the development stage towards commercialization, we will need to expand our organization, including adding marketing and sales capabilities or continuing to contract with third parties to provide these capabilities for us. As our operations expand, we expect that we will also need to manage our existing and additional relationships with various collaborative partners, suppliers and other third parties. Future growth will impose significant added responsibilities on our organization, in particular on management. Our future financial performance and our ability to commercialize roxadustat and our other product candidates and to compete effectively will depend, in part, on our ability to manage any future growth effectively. To that end, we may not be able to manage our growth efforts effectively, and hire, train and integrate additional management, administrative and sales and marketing personnel, and our failure to accomplish any of these activities could prevent us from successfully growing our company.

Although FibroGen Beijing obtained regulatory approval for roxadustat in China in December 2018, we may be unable to obtain regulatory approval for our product candidates in other countries, or such approval may be delayed or limited, due to a number of factors, many of which are beyond our control.

The clinical trials and the manufacturing of our product candidates are and will continue to be, and the marketing of our product candidates will be, subject to extensive and rigorous review and regulation by numerous government authorities in the U.S. and in other countries where we intend to develop and, if approved, market any product candidates. Before obtaining regulatory approval for the commercial sale of any product candidate, we must demonstrate through extensive preclinical trials and clinical trials that the product candidate is safe and effective for use in each indication for which approval is sought. The regulatory review and approval process is expensive and requires substantial resources and time, and in general very few product candidates that enter development receive regulatory approval. In addition, our collaboration partners for roxadustat have final control over development decisions in their respective territories and they may make decisions with respect to development or regulatory authorities that delay or limit the potential approval of roxadustat, or increase the cost of development or commercialization. Accordingly, we may be unable to successfully develop or commercialize roxadustat or pamrevlumab or any of our other product candidates.

Even though FibroGen Beijing obtained regulatory approval for roxadustat in China, we have not obtained regulatory approval for any of our product candidates in other countries and it is possible that roxadustat and pamrevlumab will never receive regulatory approval in other countries. Other regulatory authorities may take actions or impose requirements that delay, limit or deny approval of roxadustat or pamrevlumab for many reasons, including, among others:

- our failure to adequately demonstrate to the satisfaction of regulatory authorities that roxadustat is safe and effective in treating anemia in CKD or that pamrevlumab is safe and effective in treating IPF, pancreatic cancer or DMD;
- our failure to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;
- the determination by regulatory authorities that additional clinical trials are necessary to demonstrate the safety and efficacy of roxadustat or pamrevlumab, or that ongoing clinical trials need to be modified in design, size, conduct or implementation;
- our product candidates may exhibit an unacceptable safety signal as they advance through clinical trials, in particular controlled Phase 3 trials;
- the clinical research organizations ("CROs") that conduct clinical trials on our behalf may take actions outside of our control that materially adversely impact our clinical trials;
- we or third party contractors manufacturing our product candidates may not maintain current good manufacturing practices ("cGMP"), successfully pass inspection or meet other applicable manufacturing regulatory requirements;
- regulatory authorities may not agree with our interpretation of the data from our preclinical trials and clinical trials;
- collaboration partners may not perform or complete their clinical programs in a timely manner, or at all; or
- principal investigators may determine that one or more serious adverse events ("SAEs"), is related or possibly related to roxadustat, and any such determination may adversely affect our ability to obtain regulatory approval, whether or not the determination is correct.

Any of these factors, many of which are beyond our control, could jeopardize our or our collaboration partners' abilities to obtain regulatory approval for and successfully market roxadustat. Because our business and operations in the near-term are almost entirely dependent upon roxadustat, any significant delays or impediments to regulatory approval could have a material adverse effect on our business and prospects.

In China, the NMPA required that FibroGen Beijing conduct three clinical studies as a post-approval commitment: (i) a post-approval safety study in 2,000 patients; (ii) a drug-intensive monitoring study in 1,000 patients; and (iii) a dosing optimization study in approximately 300 patients on dialysis. Furthermore, in the U.S., we also expect to be required to perform additional clinical trials in order to obtain approval or as a condition to maintaining approval due to post-marketing requirements. If the FDA requires a risk evaluation and mitigation strategy ("REMS"), for any of our product candidates if approved, the substantial cost and expense of complying with a REMS or other post-marketing requirements may limit our ability to successfully commercialize our product candidates.

Preclinical, Phase 1 and Phase 2 clinical trial results may not be indicative of the results that may be obtained in larger, controlled Phase 3 clinical trials required for approval.*

Clinical development is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. Success in preclinical and early clinical trials, which are often highly variable and use small sample sizes, may not be predictive of similar results in humans or in larger, controlled clinical trials, and successful results from early or small clinical trials may not be replicated or show as favorable an outcome, even if successful.

We have conducted a limited number of Phase 2 clinical trials with pamrevlumab. We have conducted a randomized placebo-controlled study in 103 IPF patients with sub-studies in an additional 57 IPF patients comparing pamrevlumab to one of two standards of care, an open-label Phase 2 dose escalation study of pamreylumab for IPF in 89 patients and a randomized double-blind placebo controlled study for liver fibrosis in subjects with hepatitis B, and we are currently conducting an open-label randomized, active-control, neoadjuvant Phase 2 trial in pancreatic cancer combining pamrevlumab with nab-paclitaxel plus gemcitabine in 37 patients. We cannot be sure that the results we have received to date from these trials will be substantiated in larger, well-controlled Phase 3 clinical trials, that larger trials will demonstrate the safety and efficacy of pamrevlumab for these or other indications, that further studies will provide benefits over existing approved products or that new safety issues will not be uncovered in further trials. In addition, while we believe that the limited animal and human studies conducted to date suggest that pamrevlumab has the potential to arrest or reverse fibrosis and reduce tumor mass in some patients or diseases, we cannot be sure that these results will be indicative of the effects of pamrevlumab in larger human trials. In addition, the IPF and pancreatic cancer patient populations are extremely ill and routinely experience SAEs, including death, which may be attributed to pamrevlumab in a manner that negatively impacts the safety profile of our product candidate. If the additional clinical trials that we are planning or are currently conducting for pamrevlumab do not show favorable efficacy results or result in safety concerns, or if we do not meet our clinical endpoints with statistical significance, or demonstrate an acceptable risk-benefit profile, we may be prevented from or delayed in obtaining regulatory approval for pamrevlumab in one or both of these indications.

In the past we developed an earlier generation product candidate aimed at treating anemia in CKD that resulted in a clinical hold for a safety signal seen in that product in Phase 2 clinical trials. The clinical hold applied to that product candidate and roxadustat was lifted for both product candidates after submission of the requested information to the FDA. While we have not seen similar safety concerns involving roxadustat to date, some of the safety concerns associated with the treatment of patients with anemia in CKD using erythropoiesis stimulating agents ("ESAs") did not emerge for many years until placebo-controlled studies had been conducted in large numbers of patients. And while the data monitoring committee for our U.S. and Europe Phase 3 anemia trials has consistently determined that our trials should continue without modification to the protocol, safety issues may still be discovered upon review of unblinded major adverse cardiac event ("MACE") or other data. The biochemical pathways that we believe are affected by roxadustat are implicated in a variety of biological processes and disease conditions, and it is possible that the use of roxadustat to treat larger numbers of patients will demonstrate unanticipated adverse effects, including possible drug interactions, which may negatively impact the safety profile, use and market acceptance of roxadustat. We studied the potential interaction between roxadustat and three statins (atorvastatin, rosuvastatin and simvastatin), which are used to lower levels of lipids in the blood. An adverse effect associated with increased statin plasma concentration is myopathy, which typically presents in a form of myalgia. The studies indicated the potential for increased exposure to those statins when roxadustat is taken simultaneously with those statins and suggested the need for statin dose reductions for patients receiving higher statin doses. We performed additional clinical pharmacology studies to evaluate if the effect of any such interaction could be minimized or eliminated by a modification of the dosing schedule that would separate the administration of roxadustat and the statin by up to 10 hours, however, such studies showed no minimization of effect. It is possible that the potential for interaction between roxadustat and statins could lead to label provisions for statins or roxadustat relating, for example, to dose scheduling or recommended statin dose limitations. In CKD patients, statin therapy is often initiated earlier than treatment for anemia, and risks of myopathy have been shown to decrease with increased time on drug. While we believe the prior statin treatment history of such patients at established doses may reduce the risk of adverse effects from any interaction with roxadustat and facilitate any appropriate dose adjustments, we cannot be sure that this will be the case.

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Our Phase 3 trials include a MACE safety endpoint, which is a composite endpoint designed to identify major safety concerns, in particular relating to cardiovascular events such as cardiovascular death, myocardial infarction and stroke. The EMA is requiring MACE+ as a safety endpoint which, in addition to the MACE components, incorporates measurements of hospitalization rates due to heart failure or unstable angina. The FDA has also informed us that the MACE endpoint will need to be evaluated separately for our Phase 3 trials in non-dialysis-dependent ("NDD")-CKD patients and our Phase 3 trials in dialysis-dependent ("DD")-CKD patients. The MACE endpoint is being evaluated in pooled analysis across Phase 3 studies of similar study populations and requires demonstration of non-inferiority relative to comparator, which means that the MACE event rate in roxadustat-treated patients must have less than a specified probability of exceeding the rate in the comparator trial by a specified hazard ratio.

The number of patients necessary in order to permit a statistical analysis with adequate ability to detect the relative risk of MACE or MACE+ events in different arms of the trial, referred to as statistical power, depends on a number of factors, including the rate at which MACE or MACE+ events occur per patient-year in the trial, treatment duration of the patients, the achieved hazard ratios, the rates of discontinuation, and the required statistical power and confidence intervals.

In addition, we cannot be sure that the potential advantages we believe roxadustat may have for treatment of patients with anemia in CKD, as compared to the use of ESAs, will be substantiated by our larger U.S. and European Phase 3 clinical trials, or that we will be able to include a discussion of such advantages in our labeling should we obtain approval. We believe that roxadustat may have certain benefits as compared to ESAs based on the data from our Phase 2 clinical trials and China Phase 3 trials conducted to date, including safety benefits, the absence of a hypertensive effect, the potential to lower cholesterol levels and the potential to correct anemia without the use of IV iron. However, our belief that roxadustat may offer those benefits is based on a limited amount of data from our clinical trials to date, and our understanding of the likely mechanisms of action for roxadustat. Some of these benefits, such as those associated with the apparent effects on blood pressure and cholesterol, are not fully understood and, even if roxadustat receives marketing approval in additional countries beyond China, we do not expect that it will be approved for the treatment of high blood pressure or high cholesterol based on the data from our Phase 3 trials, and we may not be able to refer to any such benefits in the labeling. While the data from our Phase 2 trials suggests roxadustat may reduce low-density lipoprotein ("LDL"), and reduce the ratio of LDL to high-density lipoprotein ("HDL"), the data show it may also reduce HDL, which may be a risk to patients. In addition, causes of the safety concerns associated with the use of ESAs to achieve specified target hemoglobin levels have not been fully elucidated. While we believe that the issues giving rise to these concerns with ESAs are likely due to factors other than the hemoglobin levels achieved, we cannot be certain that roxadustat will not be associated with similar, or more severe, safety concerns.

Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials after achieving positive results in early-stage development, and we may face similar setbacks. In addition, the CKD patient population has many afflictions that may cause severe illness or death, which may be attributed to roxadustat in a manner that negatively impacts the safety profile of our product candidate. The results of our completed Phase 3 clinical trials for roxadustat demonstrated efficacy, as all primary efficacy endpoints were met with statistical significance. While we have reported topline cardiovascular safety results, the analysis of these data is ongoing; there may be unanticipated safety concerns or adverse events that prevent from or delay obtaining marketing approval for roxadustat, and even if we obtain marketing approval, any sales of roxadustat may suffer.

We do not know whether our ongoing or planned clinical trials of roxadustat or pamrevlumab will need to be redesigned based on interim results, be able to achieve sufficient enrollment or be completed on schedule, if at all.*

Clinical trials can be delayed or terminated for a variety of reasons, including delay or failure to:

- address any physician or patient safety concerns that arise during the course of the trial;
- obtain required regulatory or institutional review board ("IRB") approval or guidance;
- reach timely agreement on acceptable terms with prospective CROs and clinical trial sites;
- recruit, enroll and retain patients through the completion of the trial;
- maintain clinical sites in compliance with clinical trial protocols;
- initiate or add a sufficient number of clinical trial sites; and
- manufacture sufficient quantities of product candidate for use in clinical trials.

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In addition, we could encounter delays if a clinical trial is suspended or terminated by us, by the relevant IRBs at the sites at which such trials are being conducted, or by the FDA or other regulatory authorities. A suspension or termination of clinical trials may result from any number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, changes in laws or regulations, or a principal investigator's determination that a serious adverse event could be related to our product candidates. Any delays in completing our clinical trials will increase the costs of the trial, delay the product candidate development and approval process and jeopardize our ability to commence marketing and generate revenues. Any of these occurrences may materially and adversely harm our business and operations and prospects.

Our product candidates may cause or have attributed to them undesirable side effects or have other properties that delay or prevent their regulatory approval or limit their commercial potential.

Undesirable side effects caused by our product candidates or that may be identified as related to our product candidates by physician investigators conducting our clinical trials or even competing products in development that utilize a similar mechanism of action or act through a similar biological disease pathway could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in the delay or denial of regulatory approval by the FDA or other regulatory authorities and potential product liability claims. Adverse events and SAEs that emerge during treatment with our product candidates or other compounds acting through similar biological pathways may be deemed to be related to our product candidate and may result in:

- our Phase 3 clinical trial development plan becoming longer and more extensive;
- regulatory authorities increasing the data and information required to approve our product candidates and imposing other requirements; and
- our collaboration partners terminating our existing agreements.

The occurrence of any or all of these events may cause the development of our product candidates to be delayed or terminated, which could materially and adversely affect our business and prospects. Refer to "Business — Our Development Program for Roxadustat" and "Business — Pamrevlumab for the Treatment of Fibrosis and Cancer" for a discussion of the adverse events and SAEs that have emerged in clinical trials of roxadustat and pamrevlumab.

Clinical trials of our product candidates may not uncover all possible adverse effects that patients may experience.

Clinical trials are conducted in representative samples of the potential patient population, which may have significant variability. Clinical trials are by design based on a limited number of subjects and of limited duration for exposure to the product used to determine whether, on a potentially statistically significant basis, the planned safety and efficacy of any product candidate can be achieved. As with the results of any statistical sampling, we cannot be sure that all side effects of our product candidates may be uncovered, and it may be the case that only with a significantly larger number of patients exposed to the product candidate for a longer duration, that a more complete safety profile is identified. Further, even larger clinical trials may not identify rare serious adverse effects or the duration of such studies may not be sufficient to identify when those events may occur. There have been other products, including ESAs, for which safety concerns have been uncovered following approval by regulatory authorities. Such safety concerns have led to labeling changes or withdrawal of ESAs products from the market. While our most advanced product candidate is chemically unique from ESAs, it or any of our product candidates may be subject to similar risks. For example, roxadustat for use in anemia in CKD is being developed to address a very diverse patient population expected to have many serious health conditions at the time of administration of roxadustat, including diabetes, high blood pressure and declining kidney function.

To date we have not seen evidence of significant safety concerns with our product candidates currently in clinical trials. Patients treated with our products, if approved, may experience adverse reactions and it is possible that the FDA or other regulatory authorities may ask for additional safety data as a condition of, or in connection with, our efforts to obtain approval of our product candidates. If safety problems occur or are identified after our product candidates reach the market, we may, or regulatory authorities may require us to amend the labeling of our products, recall our products or even withdraw approval for our products.

We may fail to enroll a sufficient number of patients in our clinical trials in a timely manner, which could delay or prevent clinical trials of our product candidates.

Identifying and qualifying patients to participate in clinical trials of our product candidates is critical to our success. The timing of our clinical trials depends on the rate at which we can recruit and enroll patients in testing our product candidates. Patients may be unwilling to participate in clinical trials of our product candidates for a variety of reasons, some of which may be beyond our control:

- severity of the disease under investigation;
- availability of alternative treatments;
- size and nature of the patient population;
- eligibility criteria for and design of the study in question;
- perceived risks and benefits of the product candidate under study;
- ongoing clinical trials of competitive agents;
- physicians' and patients' perceptions of the potential advantages of our product candidates being studied in relation to available therapies or other products under development;
- our CRO's and our trial sites' efforts to facilitate timely enrollment in clinical trials;
- patient referral practices of physicians; and
- ability to monitor patients and collect patient data adequately during and after treatment.

Patients may be unwilling to participate in our clinical trials for roxadustat due to adverse events observed in other drug treatments of anemia in CKD, and patients currently controlling their disease with existing ESAs may be reluctant to participate in a clinical trial with an investigational drug. We may not be able to successfully initiate or continue clinical trials if we cannot rapidly enroll a sufficient number of eligible patients to participate in the clinical trials required by regulatory agencies. If we have difficulty enrolling a sufficient number of patients to conduct our clinical trials as planned, we may need to delay, limit or terminate on-going or planned clinical trials, any of which could have a material and adverse effect on our business and prospects.

If we or third party manufacturers and other service providers on which we rely cannot manufacture sufficient quantities of our product candidates, or at sufficient quality, or perform other services we require, we may experience delays in development, regulatory approval, launch or commercialization.

Completion of our clinical trials and commercialization of our product candidates require access to, or development of, facilities to manufacture and manage our product candidates at sufficient yields and at commercial scale. Although we have entered into commercial supply agreements for the manufacture of some of our raw materials, we have not yet entered into commercial supply agreements with all of our third-party manufacturers. We are continuing to negotiate and expect to enter into commercial supply agreements and other supply management agreements with third-party manufacturers, but we may not be able to enter into these agreements with satisfactory terms or on a timely manner.

We have limited experience manufacturing or managing third parties in manufacturing any of our product candidates in the volumes that are expected to be necessary to support large-scale clinical trials and sales. In addition, we have limited experience forecasting supply requirements or coordinating supply chain (including export management) for launch or commercialization, which is a complex process involving our third-party manufacturers and logistics providers, and for roxadustat, our collaboration partners. We may not be able to accurately forecast supplies for commercial launch, or do so in a timely manner and our efforts to establish these manufacturing and supply chain management capabilities may not meet our requirements as to quantities, scale-up, yield, cost, potency or quality in compliance with cGMP.

We have a limited amount of roxadustat and pamrevlumab in storage, limited capacity reserved at our third-party manufacturers, and there are long lead times required to manufacture and scale-up the manufacture of additional supply, as required for both late-stage clinical trials, post-approval trials, and commercial supply. If we are unable to forecast, order or manufacture sufficient quantities of roxadustat or pamrevlumab on a timely basis, it may delay our development, launch or commercialization in some or all indications we are currently pursuing. For example, prior to agreement with regulatory authorities on the scope of our Phase 3 IPF trial design, there is uncertainty as to whether our supply plans will meet our clinical requirements in a timely manner. Any delay or interruption in the supply of our product candidates or products could have a material adverse effect on our business and operations.

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Our clinical trials must be conducted with product produced under applicable cGMP regulations. Failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. We, and even an experienced third party manufacturer, may encounter difficulties in production. Difficulties may include:

- costs and challenges associated with scale-up and attaining sufficient manufacturing yields, in particular for biologic products such as pamrevlumab, which is a monoclonal antibody;
- supply chain issues, including coordination of multiple contractors in our supply chain and securing necessary licenses (such as export licenses);
- the timely availability and shelf life requirements of raw materials and supplies;
- quality control and quality assurance;
- shortages of qualified personnel and capital required to manufacture large quantities of product;
- compliance with regulatory requirements that vary in each country where a product might be sold;
- capacity or forecasting limitations and scheduling availability in contracted facilities; and
- natural disasters, such as floods, storms, earthquakes, tsunamis, and droughts, or accidents such as fire, that affect facilities, possibly limit or postpone production, and increase costs.

The FDA and EMA will do their own benefit risk analysis and may reach a different conclusion than we or our partners have internally, and these regulatory authorities may base their approval decision on different analyses, data, and statistical methods than ours.*

Even if we believe we have achieved certain results based on a totality of the evidence, such as superiority or non-inferiority, in certain endpoints, populations or subpopulations, or using certain statistical methods of analysis, the FDA and EMA will each do their own benefit-risk analysis and may reach different conclusions, using different statistical methods, different endpoints or definitions thereof, or different patient populations or sub-populations, and regulatory authorities may change their approvability criteria based on their internal analyses and discussions with expert advisors. Regulatory authorities may approve roxadustat for fewer or more limited indications than we request, or may grant approval contingent on the performance of costly post-approval clinical trials. While we will present to regulatory authorities certain pre-specified and not pre-specified sub-populations and sub-group analyses (for example, incident dialysis), multiple secondary endpoints, and multiple analytical methods (such as long-term follow up analyses), including adjusted and censored data, regulatory authorities may reject these analyses, methods, or even parts of our trial design or certain data from our studies, the rationale for our pre-specified non-inferiority margins or other portions of our statistical analysis plans. In addition, even if we are able to provide positive data with respect to certain analyses, such as incident dialysis, eGFR, hepcidin, or quality of life measures, regulatory authorities may not include such claims on any approved labeling for roxadustat, which may limit the commercialization or market opportunity for roxadustat. Further, initial topline results reported for certain studies (such as reduction of transfusion risk or hemoglobin response in the presence of inflammation), may not be representative of the data seen in all studies or may not be sustained upon further analyses or after more wide-spread use upon commercialization. The failure to obtain regulatory approval, or any label, population or other approval limitations in any jurisdiction, may significantly limit our ability to generate revenues, and any failure to obtain such approval for all of the indications and labeling claims we deem desirable could reduce our potential revenue.

Positive topline results from our Phase 3 clinical trials assessing the safety and efficacy of roxadustat may not be indicative of additional results or results for roxadustat in other indications.*

There are multiple key and secondary endpoints as well as sub-group analyses in both dialysis and non-dialysis in the U.S. and multiple secondary endpoints in addition to MACE+ as well as sub-group analyses in dialysis and non-dialysis in Europe. We continue to analyze these additional endpoints from the Phase 3 clinical trials of roxadustat in anemia of CKD, as well as from the pooled analyses, some of which may have a bearing on the safety or efficacy of roxadustat. The topline results we have reported thus far may not be indicative of these additional results. In addition, results in these CKD-anemia indications may not be indicative of our clinical trials in other indications or the safety, efficacy, or approvability of roxadustat in other indications.

Even if we are able to obtain regulatory approval of our product candidates, the label we obtain may limit the indicated uses for which our product candidates may be marketed.*

With respect to roxadustat, regulatory approvals, if obtained at all, could limit the approved indicated uses for which roxadustat may be marketed. For example, ESAs have been subject to significant safety limitations on usage as directed by the "Black Box" warnings included in their labels. Refer to "Business — Roxadustat for the Treatment of Anemia in Chronic Kidney Disease — Limitations of the Current Standard of Care for Anemia in CKD" in our annual report on Form 10-K for the year ended December 31, 2018. In addition, in the past, an approved ESA was voluntarily withdrawn due to serious safety issues discovered after approval. The safety concerns relating to ESAs may result in labeling for roxadustat containing similar warnings even if our Phase 3 clinical trials do not suggest that roxadustat has similar safety issues. Even if the label for roxadustat does not contain all of the warnings contained in the "Black Box" warning for ESAs, the label for roxadustat may contain other warnings or limit the market opportunity or approved indications for roxadustat. These warnings could include warnings against exceeding specified hemoglobin targets and other warnings that derive from the lack of clarity regarding the safety issues associated with ESAs, even if our Phase 3 clinical trials do not themselves raise safety concerns.

As an organization, we have not successfully commercialized any drug product. Therefore, we may not be able to efficiently execute our development and commercialization plans.

We are currently conducting Phase 2 clinical trials for pamrevlumab and plan on initiating Phase 3 clinical trials for pamrevlumab in the future. We have initiated Phase 3 clinical trials of roxadustat. The conduct of Phase 3 clinical trials and the submission of a successful NDA is a complicated process. As an organization, we have not completed a Phase 3 clinical trial before outside of China, where we received marketing authorization in December 2018 from the NMPA for the treatment of anemia caused by CKD in dialysis patients. We have limited experience in preparing, submitting and prosecuting regulatory filings, and have not received approval for an NDA before outside of China. Consequently, we may be unable to successfully and efficiently execute and complete necessary clinical trials in a way that leads to NDA submission and approval of roxadustat or for any other product candidate we are developing, even if our earlier stage clinical trials are successful. We may require more time and incur greater costs than our competitors and may not succeed in obtaining regulatory approvals of product candidates that we develop. Failure to commence or complete, or delays in, our planned clinical trials would prevent us from or delay us in commercializing roxadustat or any other product candidate we are developing.

In addition, in order for any Phase 3 clinical trial to support an NDA submission for approval, the FDA and foreign regulatory authorities require compliance with regulations and standards, including good clinical practices ("GCP") requirements for designing, conducting, monitoring, recording, analyzing, and reporting the results of clinical trials to ensure that the data and results from trials are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. Although we rely on third parties to conduct our clinical trials, we as the sponsor remain responsible for ensuring that each of these clinical trials is conducted in accordance with its general investigational plan and protocol under legal and regulatory requirements, including GCP. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of our CROs, trial sites, principal investigators or other third parties fail to comply with applicable GCP requirements, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or other regulatory authorities may require us to exclude the use of patient data from our clinical trials not conducted in compliance with GCP or perform additional clinical trials before approving our marketing applications. They may even reject our application for approval or refuse to accept our future applications for an extended time period. For example in China in March 2016, the State Drug Administration, now known as the NMPA issued guidance related to its clinical trial data integrity regulations. While trial sites and CROs bear liability for the accuracy and authenticity of data they are directly responsible for, the sponsor ultimately bears full responsibility for submitted clinical data and the drug application dossier. Fraudulent clinical data could result in a ban in China of a sponsor's product-related NDA applications for three years and other NDA applications for one year. We have taken extensive steps to ensure the integrity of our China clinical data. In China, the clinical site inspections confirmed our compliance with GCP regulations and supported our approval. However, we cannot assure you that upon inspection by a regulatory authority in other regions, such regulatory authority will determine that any of our clinical trials comply with GCP requirements or that our results will be deemed authentic or may be used in support of our regulatory submissions.

If we are unable to establish sales, marketing and distribution capabilities or enter into or maintain agreements with third parties to market and sell our product candidates, we may not be successful in commercializing our product candidates if and when they are approved.

We do not have a sales or marketing infrastructure and have no experience in the sales, marketing or distribution of pharmaceutical products in any country. To achieve commercial success for any product for which we obtain marketing approval, we will need to establish sales and marketing capabilities or make and maintain our existing arrangements with third parties to perform these services at a level sufficient to support our commercialization efforts.

To the extent that we would undertake sales and marketing of any of our products directly, there are risks involved with establishing our own sales, marketing and distribution capabilities. Factors that may inhibit our efforts to commercialize our products on our own include:

- our inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future products;
- our inability to effectively manage geographically dispersed sales and marketing teams;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

With respect to roxadustat, we are dependent on the commercialization capabilities of our collaboration partners, AstraZeneca and Astellas. If either such partner were to terminate its agreement with us, we would have to commercialize on our own or with another third party. We will have limited or little control over the commercialization efforts of such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products, if any, effectively. If they are not successful in commercializing our product candidates, our business and financial condition would suffer.

We face substantial competition, which may result in others discovering, developing or commercializing products before, or more successfully, than we do.*

The development and commercialization of new pharmaceutical products is highly competitive. Our future success depends on our ability to achieve and maintain a competitive advantage with respect to the development and commercialization of our product candidates. Our objective is to discover, develop and commercialize new products with superior efficacy, convenience, tolerability, and safety. We expect that in many cases, the products that we commercialize will compete with existing, market-leading products of companies that have large, established commercial organizations.

If roxadustat is approved and launched commercially, competing drugs are expected to include ESAs, particularly in those patient segments where ESAs are used. Currently available ESAs include epoetin alfa (EPOGEN ®, marketed by Amgen Inc. in the U.S., Procrit ® and Erypo ®/Eprex ®, marketed by Johnson & Johnson Inc., and Espo ® marketed by Kyowa Hakko Kirin in Japan and China), darbepoetin (Amgen/Kyowa Hakko Kirin's Aranesp ® and NESP ®) and Mircera ® marketed by Hoffmann-La Roche ("Roche") outside of the U.S. and by Vifor Pharma ("Vifor"), a Roche licensee, in the U.S. and Puerto Rico, as well as biosimilar versions of these currently marketed ESA products. ESAs have been used in the treatment of anemia in CKD for more than 20 years, serving a significant majority of DD-CKD patients. While NDD-CKD patients who are not under the care of nephrologists, including those with diabetes and hypertension, do not typically receive ESAs and are often left untreated, some patients under nephrology care may be receiving ESA therapy. It may be difficult to encourage healthcare providers and patients to switch to roxadustat from products with which they have become familiar.

We may also face competition from potential new anemia therapies currently in clinical development, including in those patient segments not currently addressed by ESAs. Companies such as GlaxoSmithKline plc ("GSK"), Bayer Corporation ("Bayer"), Akebia Therapeutics, Inc. ("Akebia"), and Japan Tobacco, are currently developing HIF prolyl hydroxylase ("HIF-PH") inhibitors for anemia in CKD indications. Akebia is currently conducting Phase 3 studies in NDD–CKD and DD-CKD, as well as additional Phase 1 and Phase 2 studies. In Japan, Mitsubishi Tanabe Pharmaceutical Corporation, Akebia's collaboration partner, is conducting Japan Phase 3 studies. GSK is conducting global Phase 3 studies in NDD-CKD and DD-CKD. In Japan, GSK has completed two Phase 3 studies in DD-CKD and is conducting a Phase 3 study in NDD-CKD. GSK and Kyowa Hakko Kirin announced in November 2018 that the two companies signed a strategic commercialization deal in Japan for daprodustat. Bayer has completed global Phase 2 studies and announced in May 2017 its HIF-PH inhibitor is now in continued development in Japan only, and its Japan Phase 3 studies in NDD-CKD and DD-CKD are underway. Japan Tobacco is also conducting Phase 3 studies in NDD-CKD and DD-CKD in Japan only. Some of these product candidates may enter the market prior to roxadustat.

In addition, there are other companies developing biologic therapies for the treatment of other anemia indications that we may also seek to pursue in the future, including anemia of MDS. For example, Acceleron Pharma Inc. and its partner Celgene Corporation ("Celgene") announced in April 2019 that Celgene has submitted a Biologics License Application ("BLA") for luspatercept for the treatment of adult patients with 1) very low to intermediate risk of MDS-associated anemia who have ring sideroblasts and require red blood cell transfusions, and 2) beta-thalassemia-associated anemia who require red blood cell transfusions. Celgene's plan to submit a marketing approval application for luspatercept in the European Union ("EU") in the second quarter of 2019. There may also be new therapies for renal-related diseases that could limit the market or level of reimbursement available for roxadustat if and when it is commercialized.

In China, biosimilars of epoetin alfa are offered by Chinese pharmaceutical companies such as EPIAO marketed by 3SBio Inc. as well as more than 15 other local manufacturers. We may also face competition by HIF-PH inhibitors from other companies such as Akebia, Bayer, and GSK, which was authorized by the NMPA to conduct trials in China to support its ex-China regulatory filings. Furthermore, while it is too early to understand how the NMPA will implement its recently approved guidelines to allow multinational companies to use their ex-China clinical data in their NDAs in China, these guidelines could in theory allow competitors to accelerate their NDA applications in China. Akebia announced in December 2015 that it has entered into a development and commercialization partnership with Mitsubishi Tanabe Pharmaceutical Corporation for its HIF-PH inhibitor vadadustat in Japan, Taiwan, South Korea, India, and certain other countries in Asia, and announced in April 2017 an expansion of their U.S. collaboration with Otsuka to add markets, including China. Two Chinese domestic companies, Jiangsu Hengrui and Guangdong Sunshine, have announced they also secured the NMPA approval to conduct clinical trials for their respective HIF-PH inhibitors.

The first biosimilar ESAs, Pfizer's Retacrit® (epoetin zeta), entered the U.S. market in November 2018. Market penetration of Retacrit® (epoetin zeta) and the potential addition of other biosimilar ESAs, currently under development, may alter the competitive and pricing landscape of anemia therapy in DD-CKD patients under the end stage renal disease bundle. The patents for Amgen's epoetin alfa, EPOGEN, expired in 2004 in the EU, and the final material patents in the U.S. expired in May 2015. Several biosimilar versions of currently marketed ESAs are available for sale in the EU, China and other territories. In the U.S., a few ESA biosimilars are currently under development. Sandoz, a division of Novartis, markets Binocrit® (epoetin alfa) in Europe and may file a biosimilar BLA in the U.S.

The majority of the current CKD anemia market focuses on dialysis patients, who visit dialysis centers on a regular basis, typically three-times a week, and anemia therapies are administered as part of the visit. Two of the largest operators of dialysis clinics in the U.S., DaVita Healthcare Partners Inc. ("DaVita") and Fresenius Medical Care AG & Co. KGaA ("Fresenius"), collectively provide dialysis care to approximately 70% of U.S. dialysis patients, and therefore have historically won long-term contracts including rebate terms with Amgen. In January 2017, DaVita entered into a new 6-year sourcing and supply agreement with Amgen that is effective through 2022. Fresenius' contract with Amgen expired in 2015, and Fresenius is now administering Mircera® in a significant portion of its U.S. dialysis patients since Mircera was made available by Vifor. Successful penetration of this market may require a significant agreement with Fresenius or DaVita on favorable terms and on a timely basis.

If pamrevlumab is approved and launched commercially to treat IPF, competing drugs are expected to include Roche's Esbriet® (pirfenidone) and Boehringer Ingelheim Pharma GmbH & Co. KG's Ofev® (nintedanib). Nintedanib is also in development for non-small cell lung cancer and ovarian cancer. Other potential competitive product candidates in development for IPF include Biogen-Idec's BG-00011, Galapagos NV's GLPG1690, Kadmon Holdings, Inc.'s KD025, Prometic Life Sciences Inc.'s PBI-4050, and Promedior Inc.'s PRM-151. Galapagos initiated a Phase 3 study for GLPG 1690 in December 2018.

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If pamrevlumab is approved and launched commercially to treat locally advanced pancreatic cancer patients who are not candidates for surgical resection, pamrevlumab may face competition from agents seeking approval in combination with gemcitibine and nab-paclitaxel from companies such as NewLink Genetics Corporation and Halozyme Therapeutics, Inc. Gemcitabine and/or nab-paclitaxel are the current standard of care in the first-line treatment of metastatic pancreatic cancer. Celgene Corporation's Abraxane® (nab-paclitaxel) was launched in the U.S. and Europe in 2013 and 2014, and was the first drug approved in this disease in nearly a decade.

If pamrevlumab is approved and launched commercially to treat DMD, pamrevlumab may face competition for some patients from Sarepta Therapeutics, Inc. ("Sarepta"), as well as PTC Therapeutics, Santhera Pharmaceuticals, and Catabasis Pharmaceuticals.

Sarepta is researching and developing clinical candidates for many of the specific mutations in the dystrophin gene and received accelerated approval in the U.S. for its first, drug Exondys 51® (eteplirsen) for patients who have a confirmed mutation in the DMD gene that is amenable to exon 51 skipping. This mutation represents a subset of approximately 13% of patients with DMD. Sarepta recently received a negative opinion from the European Medicine ("EMA") regarding its eteplirsen application in September 2018. In addition to etepliresen, Sarepta has two additional exon skipping programs in Phase 3 development, each of which targets approximately 8% of patients with DMD. Sarepta is also developing gene therapies for the treatment of DMD and reported positive preliminary results from a Phase 1/2a program in June 2018.

Marathon Pharmaceuticals received approval for its drug Emflaza (deflazacort) on February 9, 2017 and on March 16, 2017 announced that it had sold the commercialization rights to Emflaza to PTC Therapeutics.

PTC Therapeutics' product ataluren (Translarna TM) received conditional approval in Europe in 2014, which was renewed in November 2016 with a request for a new randomized placebo-controlled 18-month study by the Committee for Medicinal Products for Human Use of the EMA, while the FDA stated in its complete response letter in October of 2017 that the FDA is unable to approve the application in its current form. Translarna targets a different set of DMD patients from those being targeted by Sarepta's existing exonskipping therapeutic candidate; however, it is also limited to a subset of patients who carry a specific mutation.

While pamrevlumab and some other potential competitors are intended to treat DMD patients regardless of the specific mutation, there can be no assurance that clinical trials will support broadly treating DMD patients. For example, Santhera Pharmaceuticals reported positive Phase 3 data with its drug idebenone (Raxone ®/Catena ®) in a trial measuring changes in lung function for DMD patients, however the EMA rejected the application and the FDA has asked for additional data from an ongoing trial prior to considering Raxone for approval. Santhera is currently conducting the additional Phase 3 study in the U.S. and Europe.

Catabasis Pharmaceuticals reported in April 2018 positive Phase 2 data from its clinical trial candidate edasalonexent. Edasalonexent was reported to have preserved muscle function and slowed the progression of DMD compared to rates of change in the control period prior to treatment with edasalonexent. The company started a single placebo controlled Phase 3 trial in September 2018. Catabasis expects topline data from this trial in the second quarter of 2020, and NDA filing in 2021.

The success of any or all of these potential competitive products may negatively impact the development and potential for success of pamrevlumab. In addition, any competitive products that are on the market or in development may compete with pamrevlumab for patient recruitment and enrollment for clinical trials or may force us to change our clinical trial design, including, in order to compare pamrevlumab against another drug, which may be the new standard of care.

If FG-5200 is approved and launched in China to treat corneal blindness resulting from partial thickness corneal damage without active inflammation and infection, it is likely to compete with other products designed to treat corneal damage. For example, in April 2015, a subsidiary of China Regenerative Medicine International Limited received approval for their acellular porcine cornea stroma medical device to treat patients in China with corneal ulcers and in April 2016, Guangzhou Yourvision Biotech Co. Ltd, a subsidiary of Guanhao Biotech, received approval for their acellular porcine cornea medical device to treat patients in China with infectious keratitis that does not respond to drug treatment.

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Moreover, many of our competitors have significantly greater resources than we do. Large pharmaceutical companies, in particular, have extensive experience in clinical testing, obtaining regulatory approvals, recruiting patients, manufacturing pharmaceutical products, and commercialization. In the potential anemia market for roxadustat, for example, large and established companies such as Amgen and Roche, among others, compete aggressively to maintain their market shares. In particular, the currently marketed ESA products are supported by large pharmaceutical companies that have greater experience and expertise in commercialization in the anemia market, including in securing reimbursement, government contracts and relationships with key opinion leaders; conducting testing and clinical trials; obtaining and maintaining regulatory approvals and distribution relationships to market products; and marketing approved products. These companies also have significantly greater scale research and marketing capabilities than we do and may also have products that have been approved or are in later stages of development, and have collaboration agreements in our target markets with leading dialysis companies and research institutions. These competitors have in the past successfully prevented new and competing products from entering the anemia market, and we expect that their resources will represent challenges for us and our collaboration partners, AstraZeneca and Astellas. If we and our collaboration partners are not able to compete effectively against existing and potential competitors, our business and financial condition may be materially and adversely affected.

Our future commercial success depends upon attaining significant market acceptance of our product candidates, if approved, among physicians, patients, third party payors and others in the health care community.

Even if we obtain marketing approval for roxadustat, pamrevlumab or any other product candidates that we may develop or acquire in the future in all indications and geographic regions, these product candidates may not gain market acceptance among physicians, third party payors, patients and others in the health care community. Market acceptance of any approved product, including in roxadustat for the treatment of anemia caused by CKD in dialysis patients in China, depends on a number of other factors, including:

- the clinical indications for which the product is approved and the labeling required by regulatory authorities for use with the product, including any warnings that may be required in the labeling;
- acceptance by physicians and patients of the product as a safe and effective treatment and the willingness of the target patient population to try new therapies and of physicians to prescribe new therapies;
- the cost, safety, efficacy and convenience of treatment in relation to alternative treatments;
- the restrictions on the use of our products together with other medications, if any;
- the availability of adequate coverage and reimbursement or pricing by third party payors and government authorities;
- the ability of treatment providers, such as dialysis clinics, to enter into relationships with us without violating their existing agreement; and
- the effectiveness of our sales and marketing efforts.

No or limited reimbursement or insurance coverage of our approved products, if any, by third party payors may render our products less attractive to patients and healthcare providers.

Market acceptance and sales of any approved products will depend significantly on reimbursement or coverage of our products by the Chinese government or third party payors, and may be affected by existing and future healthcare reform measures or prices of related products for which the government or third party reimbursement applies. Coverage and reimbursement by the government or a third party payor may depend upon a number of factors, including the payor's determination that use of a product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

The review and publication cycle for the Chinese government to update their reimbursement lists (national or provincial) is unpredictable and is outside our control.

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Obtaining coverage and reimbursement approval for a product from a government or other third party payor is a time consuming and costly process that could require us to provide supporting scientific, clinical and cost-effectiveness data for the use of our products to the payor, which we may not be able to provide. Furthermore, the reimbursement policies of third party payors may significantly change in a manner that renders our clinical data insufficient for adequate reimbursement or otherwise limits the successful marketing of our products. Even if we obtain coverage for our product candidates, third party payors may not establish adequate reimbursement amounts, which may reduce the demand for, or the price of, our products. If reimbursement is not available or is available only to limited levels, we may not be able to commercialize certain of our products.

Price controls may limit the price at which products such as roxadustat, if approved, are sold. For example, reference pricing is used by various EU member states and parallel distribution, or arbitrage between low-priced and high-priced member states, can further reduce prices. In some countries, we or our partner may be required to conduct a clinical trial or other studies that compare the cost-effectiveness of our product candidates to other available products in order to obtain or maintain reimbursement or pricing approval. Publication of discounts by third party payors or authorities may lead to further pressure on the prices or reimbursement levels within the country of publication and other countries. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unacceptable levels, we or our partner may elect not to commercialize our products in such countries, and our business and financial condition could be adversely affected.

Risks Related to Our Reliance on Third Parties

If our collaborations with Astellas or AstraZeneca were terminated, or if Astellas or AstraZeneca were to prioritize other initiatives over their collaborations with us, whether as a result of a change of control or otherwise, our ability to successfully develop and commercialize our lead product candidate, roxadustat, would suffer.

We have entered into collaboration agreements with respect to the development and commercialization of our lead product candidate, roxadustat, with Astellas and AstraZeneca. These agreements provide for reimbursement of our development costs by our collaboration partners and also provide for commercialization of roxadustat throughout the major territories of the world.

Our agreements with Astellas and AstraZeneca provide each of them with the right to terminate their respective agreements with us, upon the occurrence of negative clinical results, delays in the development and commercialization of our product candidates or adverse regulatory requirements or guidance. The termination of any of our collaboration agreements would require us to fund and perform the further development and commercialization of roxadustat in the affected territory, or pursue another collaboration, which we may be unable to do, either of which could have an adverse effect on our business and operations. In addition, each of those agreements provides our respective partners the right to terminate any of those agreements upon written notice for convenience. Moreover, if Astellas or AstraZeneca, or any successor entity, were to determine that their collaborations with us are no longer a strategic priority, or if either of them or a successor were to reduce their level of commitment to their collaborations with us, our ability to develop and commercialize roxadustat could suffer. In addition, some of our collaborations are exclusive and preclude us from entering into additional collaboration agreements with other parties in the area or field of exclusivity.

If we fail to establish and maintain strategic collaborations related to our product candidates, we will bear all of the risk and costs related to the development and commercialization of any such product candidate, and we may need to seek additional financing, hire additional employees and otherwise develop expertise at significant cost. This in turn may negatively affect the development of our other product candidates as we direct resources to our most advanced product candidates.

Conflicts with our collaboration partners could jeopardize our collaboration agreements and our ability to commercialize product candidates.

Our collaboration partners have certain rights to control decisions regarding the development and commercialization of our product candidates with respect to which they are providing funding. If we have a disagreement over strategy and activities, our plans for obtaining approval may be revised and negatively affect the anticipated timing and potential for success of our product candidates. Even if a product under a collaboration agreement is approved, we will remain substantially dependent on the commercialization strategy and efforts of our collaboration partners, and neither of our collaboration partners has experience in commercialization of a novel drug such as roxadustat in the dialysis market.

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With respect to our collaboration agreements for roxadustat, there are additional complexities in that we and our collaboration partners, Astellas and AstraZeneca, must reach consensus on our Phase 3 development program. Multi-party decision-making is complex and involves significant time and effort, and there can be no assurance that the parties will cooperate or reach consensus, or that one or both of our partners will not ask to proceed independently in some or all of their respective territories or functional areas of responsibility in which the applicable collaboration partner would otherwise be obligated to cooperate with us. Any disputes or lack of cooperation with us by either Astellas or AstraZeneca may negatively impact the timing or success of our planned Phase 3 clinical studies.

We intend to conduct proprietary research programs in specific disease areas that are not covered by our collaboration agreements. Our pursuit of such opportunities could, however, result in conflicts with our collaboration partners in the event that any of our collaboration partners takes the position that our internal activities overlap with those areas that are exclusive to our collaboration agreements, and we should be precluded from such internal activities. Moreover, disagreements with our collaboration partners could develop over rights to our intellectual property. In addition, our collaboration agreements may have provisions that give rise to disputes regarding the rights and obligations of the parties. Any conflict with our collaboration partners could lead to the termination of our collaboration agreements, delay collaborative activities, reduce our ability to renew agreements or obtain future collaboration agreements or result in litigation or arbitration and would negatively impact our relationship with existing collaboration partners.

Certain of our collaboration partners could also become our competitors in the future. If our collaboration partners develop competing products, fail to obtain necessary regulatory approvals, terminate their agreements with us prematurely or fail to devote sufficient resources to the development and commercialization of our product candidates, the development and commercialization of our product candidates and products could be delayed.

We rely on third parties for the conduct of most of our preclinical and clinical trials for our product candidates, and if our third party contractors do not properly and successfully perform their obligations under our agreements with them, we may not be able to obtain or may be delayed in receiving regulatory approvals for our product candidates.

We rely heavily on university, hospital, dialysis centers and other institutions and third parties, including the principal investigators and their staff, to carry out our clinical trials in accordance with our clinical protocols and designs. We also rely on a number of third party CROs to assist in undertaking, managing, monitoring and executing our ongoing clinical trials, including those for roxadustat. We expect to continue to rely on CROs, clinical data management organizations, medical institutions and clinical investigators to conduct our development efforts in the future, including our Phase 3 development program for roxadustat. We compete with many other companies for the resources of these third parties, and large pharmaceutical companies often have significantly more extensive agreements and relationships with such third party providers, and such third party providers may prioritize the requirements of such large pharmaceutical companies over ours. The third parties on whom we rely may terminate their engagements with us at any time, which may cause delay in the development and commercialization of our product candidates. If any such third party terminates its engagement with us or fails to perform as agreed, we may be required to enter into alternative arrangements, which would result in significant cost and delay to our product development program. Moreover, our agreements with such third parties generally do not provide assurances regarding employee turnover and availability, which may cause interruptions in the research on our product candidates by such third parties.

Moreover, while our reliance on these third parties for certain development and management activities will reduce our control over these activities, it will not relieve us of our responsibilities. For example, the FDA and foreign regulatory authorities require compliance with regulations and standards, including GCP requirements for designing, conducting, monitoring, recording, analyzing and reporting the results of clinical trials to ensure that the data and results from trials are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. Although we rely on third parties to conduct our clinical trials, we, as the sponsor, remain responsible for ensuring that each of these clinical trials is conducted in accordance with its general investigational plan and protocol under legal and regulatory requirements, including GCP. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, principal investigators and trial sites.

If any of our CROs, trial sites, principal investigators or other third parties fail to comply with applicable GCP requirements, other regulations, trial protocol or other requirements under their agreements with us, the quality or accuracy of the data they obtain may be compromised or unreliable, and the trials of our product candidates may not meet regulatory requirements. If trials do not meet regulatory requirements or if these third parties need to be replaced, the development of our product candidates may be delayed, suspended or terminated, regulatory authorities may require us to exclude the use of patient data from our approval applications or perform additional clinical trials before approving our marketing applications. Regulatory authorities may even reject our application for approval or refuse to accept our future applications for an extended time period. We cannot assure that upon inspection by a regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP requirements or that our results may be used in support of our regulatory submissions. If any of these events occur, we may not be able to obtain regulatory approval for our product candidates on a timely basis, at a reasonable cost, or at all.

We currently rely, and expect to continue to rely, on third parties to conduct many aspects of our clinical studies and product manufacturing, and these third parties may not perform satisfactorily.

We do not have operating manufacturing facilities at this time other than our roxadustat and FG-5200 manufacturing facility in China, and our current commercial manufacturing facility plans in China are not expected to satisfy the requirements necessary to support development and commercialization outside of China. Other than in and for China specifically, we do not expect to independently manufacture our products. We currently rely, and expect to continue to rely, on third parties to scale-up, manufacture and supply roxadustat and our other product candidates outside of China. Risks arising from our reliance on third party manufacturers include:

- reduced control and additional burdens of oversight as a result of using third party manufacturers for all aspects of manufacturing activities, including regulatory compliance and quality control and quality assurance;
- termination of manufacturing agreements, termination fees associated with such termination, or nonrenewal of manufacturing agreements with third parties may negatively impact our planned development and commercialization activities;
- the possible misappropriation of our proprietary technology, including our trade secrets and know-how; and
- disruptions to the operations of our third party manufacturers or suppliers unrelated to our product, including the merger, acquisition, or bankruptcy of a manufacturer or supplier or a catastrophic event affecting our manufacturers or suppliers.

Any of these events could lead to development delays or failure to obtain regulatory approval, or affect our ability to successfully commercialize our product candidates. Some of these events could be the basis for action by the FDA or another regulatory authority, including injunction, recall, seizure or total or partial suspension of production.

The facilities used by our contract manufacturers to manufacture our product candidates must pass inspections by the FDA and other regulatory authorities. Although, except for China, we do not control the manufacturing operations of, and expect to remain completely dependent on, our contract manufacturers for manufacture of drug substance and finished drug product, we are ultimately responsible for ensuring that our product candidates are manufactured in compliance with cGMP requirements. If our contract manufacturers cannot successfully manufacture material that conforms to our or our collaboration partners' specifications, or the regulatory requirements of the FDA or other regulatory authorities, we may not be able to secure and/or maintain regulatory approval for our product candidates and our development or commercialization plans may be delayed. In addition, we have no control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. In addition, although our longer-term agreements are expected to provide for requirements to meet our quantity and quality requirements to manufacture our products candidates for clinical studies and commercial sale, we will have minimal direct control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel and we expect to rely on our audit rights to ensure that those qualifications are maintained to meet our requirements. If our contract manufacturers' facilities do not pass inspection by regulatory authorities, or if regulatory authorities do not approve these facilities for the manufacture of our products, or withdraw any such approval in the future, we would need to identify and qualify alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our products, if approved. Moreover, any failure of our third party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us or adverse regulatory consequences, including clinical holds, warnings or untitled letters, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which would be expected to significantly and adversely affect supplies of our products to us and our collaboration partners.

Any of our third party manufacturers may terminate their engagement with us at any time and we have not yet entered into any commercial supply agreements for the manufacture of active pharmaceutical ingredients ("APIs") or drug products. With respect to roxadustat, AstraZeneca and Astellas have certain rights to assume manufacturing of roxadustat and the existence of those rights may limit our ability to enter into favorable long-term supply agreements, if at all, with other third party manufacturers. In addition, our product candidates and any products that we may develop may compete with other product candidates and products for access and prioritization to manufacture. Certain third party manufacturers may be contractually prohibited from manufacturing our product due to non-compete agreements with our competitors or a commitment to grant another party priority relative to our products. There are a limited number of third party manufacturers that operate under cGMP and that might be capable of manufacturing to meet our requirements. Due to the limited number of third party manufacturers with the contractual freedom, expertise, required regulatory approvals and facilities to manufacture our products on a commercial scale, identifying and qualifying a replacement third party manufacturer would be expensive and time-consuming and may cause delay or interruptions in the production of our product candidates or products, which in turn may delay, prevent or impair our development and commercialization efforts.

We have a letter agreement with IRIX Pharmaceuticals, Inc. ("IRIX"), a third party manufacturer that we have used in the past, pursuant to which we agreed to negotiate a single source manufacturing agreement that included a right of first negotiation for the cGMP manufacture of HIF-PH inhibitors, including roxadustat, provided that IRIX is able to match any third party bids within 5%. The exclusive right to manufacture extends for five years after approval of an NDA for those compounds, and any agreement would provide that no minimum amounts would be specified until appropriate by forecast and that we and a commercialization partner would have the rights to contract with independent third parties that exceed IRIX's internal manufacturing capabilities or in the event that we or our commercialization partner determines for reasons of continuity of supply and security that such a need exists, provided that IRIX would supply no less than 65% of the product if it is able to provide this level of supply. Subsequent to the letter agreement, we and IRIX have entered into several additional service agreements. IRIX has requested in writing that we honor the letter agreement with respect to the single source manufacturing agreement, and if we were to enter into any such exclusive manufacturing agreement, there can be no assurance that IRIX will not assert a claim for right to manufacture roxadustat or that IRIX could manufacture roxadustat successfully and in accordance with applicable regulations for a commercial product and the specifications of our collaboration partners. In 2015, Patheon Pharmaceuticals Inc., a business unit of DPx Holdings B.V. ("Patheon"), acquired IRIX, and in 2017 ThermoFisher Scientific Inc. acquired Patheon.

If any third party manufacturer terminates its engagement with us or fails to perform as agreed, we may be required to find replacement manufacturers, which would result in significant cost and delay to our development programs. Although we believe that there are several potential alternative manufacturers who could manufacture our product candidates, we may incur significant delays and added costs in identifying, qualifying and contracting with any such third party or potential second source manufacturer. In any event, with any third party manufacturer we expect to enter into technical transfer agreements and share our know-how with the third party manufacturer, which can be time-consuming and may result in delays. These delays could result in a suspension or delay of marketing roxadustat.

Certain of the components of our product candidates are acquired from single-source suppliers and have been purchased without long-term supply agreements. The loss of any of these suppliers, or their failure to supply us with supplies of sufficient quantity and quality to complete our drug substance or finished drug product of acceptable quality and an acceptable price, would materially and adversely affect our business.

We do not have an alternative supplier of certain components of our product candidates. To date, we have used purchase orders for the supply of materials that we use in our product candidates. We may be unable to enter into long-term commercial supply arrangements with our vendors, or do so on commercially reasonable terms, which could have a material adverse impact upon our business. In addition, we currently rely on our contract manufacturers to purchase from third-party suppliers some of the materials necessary to produce our product candidates. We do not have direct control over the acquisition of those materials by our contract manufacturers. Moreover, we currently do not have any agreements for the commercial production of those materials.

The logistics of our supply chain, which include shipment of materials and intermediates from countries such as China and India add additional time and risk to the manufacture of our product candidates. While we have in the past maintained sufficient inventory of materials, API, and drug product to meet our and our collaboration partners' needs for roxadustat to date, the lead time and regulatory approvals required to source from and into countries outside of the U.S. increase the risk of delay and potential shortages of supply.

Risks Related to Our Intellectual Property

If our efforts to protect our proprietary technologies are not adequate, we may not be able to compete effectively in our market.

We rely upon a combination of patents, trade secret protection and contractual arrangements to protect the intellectual property related to our technologies. We will only be able to protect our products and proprietary information and technology by preventing unauthorized use by third parties to the extent that our patents, trade secrets, and contractual position allow us to do so. Any disclosure to or misappropriation by third parties of our trade secrets or confidential information could compromise our competitive position. Moreover, we are involved in, have in the past been involved in, and may in the future be involved in legal or administrative proceedings involving our intellectual property initiated by third parties, and which proceedings can result in significant costs and commitment of management time and attention. As our product candidates continue in development, third parties may attempt to challenge the validity and enforceability of our patents and proprietary information and technologies.

We also are involved in, have in the past been involved in, and may in the future be involved in initiating legal or administrative proceedings involving the product candidates and intellectual property of our competitors. These proceedings can result in significant costs and commitment of management time and attention, and there can be no assurance that our efforts would be successful in preventing or limiting the ability of our competitors to market competing products.

Composition-of-matter patents relating to the API are generally considered to be the strongest form of intellectual property protection for pharmaceutical products, as such patents provide protection not limited to any one method of use. Method-of-use patents protect the use of a product for the specified method(s), and do not prevent a competitor from making and marketing a product that is identical to our product for an indication that is outside the scope of the patented method. We rely on a combination of these and other types of patents to protect our product candidates, and there can be no assurance that our intellectual property will create and sustain the competitive position of our product candidates.

Biotechnology and pharmaceutical product patents involve highly complex legal and scientific questions and can be uncertain. Any patent applications that we own or license may fail to result in issued patents. Even if patents do successfully issue from our applications, third parties may challenge their validity or enforceability, which may result in such patents being narrowed, invalidated, or held unenforceable. Even if our patents and patent applications are not challenged by third parties, those patents and patent applications may not prevent others from designing around our claims and may not otherwise adequately protect our product candidates. If the breadth or strength of protection provided by the patents and patent applications we hold with respect to our product candidates is threatened, competitors with significantly greater resources could threaten our ability to commercialize our product candidates. Discoveries are generally published in the scientific literature well after their actual development, and patent applications in the U.S. and other countries are typically not published until 18 months after their filing, and in some cases are never published. Therefore, we cannot be certain that we or our licensors were the first to make the inventions claimed in our owned and licensed patents or patent applications, or that we or our licensors were the first to file for patent protection covering such inventions. Subject to meeting other requirements for patentability, for U.S. patent applications filed prior to March 16, 2013, the first to invent the claimed invention is entitled to receive patent protection for that invention while, outside the U.S., the first to file a patent application encompassing the invention is entitled to patent protection for the invention. The U.S. moved to a "first to file" system under the Leahy-Smith America Invents Act ("AIA"), effective March 16, 2013. This system also includes procedures for challenging issued patents and pending patent applications, which creates additional uncertainty. We may become involved in opposition or interference proceedings challenging our patents and patent applications or the patents and patent applications of others, and the outcome of any such proceedings are highly uncertain. An unfavorable outcome in any such proceedings could reduce the scope of or invalidate our patent rights, allow third parties to commercialize our technology and compete directly with us, or result in our inability to manufacture, develop or commercialize our product candidates without infringing the patent rights of others.

In addition to the protection afforded by patents, we seek to rely on trade secret protection and confidentiality agreements to protect proprietary know-how, information, or technology that is not covered by our patents. Although our agreements require all of our employees to assign their inventions to us, and we require all of our employees, consultants, advisors and any third parties who have access to our trade secrets, proprietary know-how and other confidential information and technology to enter into appropriate confidentiality agreements, we cannot be certain that our trade secrets, proprietary know-how and other confidential information and technology will not be subject to unauthorized disclosure or that our competitors will not otherwise gain access to or independently develop substantially equivalent trade secrets, proprietary know-how and other information and technology. Furthermore, the laws of some foreign countries, in particular, China, where we have operations, do not protect proprietary rights to the same extent or in the same manner as the laws of the U.S. As a result, we may encounter significant problems in protecting and defending our intellectual property globally. If we are unable to prevent unauthorized disclosure of our intellectual property related to our product candidates and technology to third parties, we may not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business and operations.

Intellectual property disputes with third parties and competitors may be costly and time consuming, and may negatively affect our competitive position.

Our commercial success may depend on our avoiding infringement of the patents and other proprietary rights of third parties as well as on enforcing our patents and other proprietary rights against third parties. Pharmaceutical and biotechnology intellectual property disputes are characterized by complex, lengthy and expensive litigation over patents and other intellectual property rights. We may initiate or become party to or be threatened with future litigation or other proceedings regarding intellectual property rights with respect to our product candidates and competing products.

As our product candidates progress toward commercialization, we or our collaboration partners may be subject to patent infringement claims from third parties. We attempt to ensure that our product candidates do not infringe third party patents and other proprietary rights. However, the patent landscape in competitive product areas is highly complex, and there may be patents of third parties of which we are unaware that may result in claims of infringement. Accordingly, there can be no assurance that our product candidates do not infringe proprietary rights of third parties, and parties making claims against us may seek and obtain injunctive or other equitable relief, which could potentially block further efforts to develop and commercialize our product candidates including roxadustat or pamrevlumab. Any litigation involving defense against claims of infringement, regardless of the merit of such claims, would involve substantial litigation expense and would be a substantial diversion of management time.

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We intend, if necessary, to vigorously enforce our intellectual property in order to protect the proprietary position of our product candidates, including roxadustat and pamrevlumab. Active efforts to enforce our patents may include litigation, administrative proceedings, or both, depending on the potential benefits that might be available from those actions and the costs associated with undertaking those efforts against third parties. We carefully review and monitor publicly available information regarding products that may be competitive with our product candidates and assert our intellectual property rights where appropriate. We previously prevailed in an administrative challenge initiated by a major biopharmaceutical company regarding our intellectual property rights, maintaining our intellectual property in all relevant scope, and will continue to protect and enforce our intellectual property rights. Moreover, third parties may continue to initiate new proceedings in the U.S. and foreign jurisdictions to challenge our patents from time to time.

We may consider administrative proceedings and other means for challenging third party patents and patent applications. An unfavorable outcome in any such challenge could require us to cease using the related technology and to attempt to license rights to it from the prevailing third party, which may not be available on commercially reasonable terms, if at all, in which case our business could be harmed.

Third parties may also challenge our patents and patent applications, through interference, reexamination, inter partes review, and postgrant review proceedings before the U.S. Patent and Trademark Office ("USPTO") or through comparable proceedings in other territories. For example, Akebia and others have filed oppositions against certain European patents within our HIF Anemia-related Technologies Patent Portfolio. In three of these proceedings, for FibroGen European Patent Nos. 1463823, 1633333, and 2322155, the European Patent Office has handed down decisions unfavorable to FibroGen. In a fourth of these proceedings, the European Patent Office issued a decision favorable to FibroGen, maintaining FibroGen European Patent No. 2322153 in amended form. All of these decisions are currently under appeal, and these four patents are valid and enforceable pending resolution of the appeals. The ultimate outcomes of such proceedings remain uncertain, and ultimate resolution of the appeals may take two years or longer. In addition, Akebia recently filed oppositions against FibroGen European Patent Nos. 2289531 and 2298301. Akebia is also pursuing invalidation actions against corresponding patents in Canada and in Japan, and Akebia and GSK have initiated actions against corresponding patents in the United Kingdom. GSK has also filed for a declaration of non-infringement in UK patents corresponding to FibroGen European Patent Nos. 2322153 and 2322155. Our partner Astellas has initiated infringement actions against Akebia and GSK based on the specific UK patents challenged by each respective party in their corresponding UK actions. While we believe the ultimate outcome of all proceedings will be that these FibroGen patents will be upheld in relevant part, we note that narrowing or even revocation of any of these patents would not affect our exclusivity for roxadustat or our freedom-to-operate with respect to use of roxadustat for the treatment of anemia.

Furthermore, there is a risk that any public announcements concerning the status or outcomes of intellectual property litigation or administrative proceedings may adversely affect the price of our stock. If securities analysts or our investors interpret such status or outcomes as negative or otherwise creating uncertainty, our common stock price may be adversely affected.

Our reliance on third parties and agreements with collaboration partners requires us to share our trade secrets, which increases the possibility that a competitor may discover them or that our trade secrets will be misappropriated or disclosed.

Our reliance on third party contractors to develop and manufacture our product candidates is based upon agreements that limit the rights of the third parties to use or disclose our confidential information, including our trade secrets and know-how. Despite the contractual provisions, the need to share trade secrets and other confidential information increases the risk that such trade secrets and information are disclosed or used, even if unintentionally, in violation of these agreements. In the highly competitive markets in which our product candidates are expected to compete, protecting our trade secrets, including our strategies for addressing competing products, is imperative, and any unauthorized use or disclosure could impair our competitive position and may have a material adverse effect on our business and operations.

In addition, our collaboration partners are larger, more complex organizations than ours, and the risk of inadvertent disclosure of our proprietary information may be increased despite their internal procedures and contractual obligations in place with our collaboration partners. Despite our efforts to protect our trade secrets and other confidential information, a competitor's discovery of such trade secrets and information could impair our competitive position and have an adverse impact on our business.

We have an extensive worldwide patent portfolio. The cost of maintaining our patent protection is high and maintaining our patent protection requires continuous review and compliance in order to maintain worldwide patent protection. We may not be able to effectively maintain our intellectual property position throughout the major markets of the world.

The USPTO and foreign patent authorities require maintenance fees and payments as well as continued compliance with a number of procedural and documentary requirements. Noncompliance may result in abandonment or lapse of the subject patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance may result in reduced royalty payments for lack of patent coverage in a particular jurisdiction from our collaboration partners or may result in competition, either of which could have a material adverse effect on our business.

We have made, and will continue to make, certain strategic decisions in balancing costs and the potential protection afforded by the patent laws of certain countries. As a result, we may not be able to prevent third parties from practicing our inventions in all countries throughout the world, or from selling or importing products made using our inventions in and into the U.S. or other countries. Third parties may use our technologies in territories in which we have not obtained patent protection to develop their own products and, further, may infringe our patents in territories which provide inadequate enforcement mechanisms, even if we have patent protection. Such third party products may compete with our product candidates, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

The laws of some foreign countries do not protect proprietary rights to the same extent as do the laws of the U.S., and we may encounter significant problems in securing and defending our intellectual property rights outside the U.S.

Many companies have encountered significant problems in protecting and defending intellectual property rights in certain countries. The legal systems of certain countries, particularly certain developing countries such as China, do not always favor the enforcement of patents, trade secrets, and other intellectual property rights, particularly those relating to pharmaceutical and biotechnology products, which could make it difficult for us to stop infringement of our patents, misappropriation of our trade secrets, or marketing of competing products in violation of our proprietary rights. In China, our intended establishment of significant operations will depend in substantial part on our ability to effectively enforce our intellectual property rights in that country. Proceedings to enforce our intellectual property rights in foreign countries could result in substantial costs and divert our efforts and attention from other aspects of our business, and could put our patents in these territories at risk of being invalidated or interpreted narrowly, or our patent applications at risk of not being granted, and could provoke third parties to assert claims against us. We may not prevail in all legal or other proceedings that we may initiate and, if we were to prevail, the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Intellectual property rights do not address all potential threats to any competitive advantage we may have.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations, and intellectual property rights may not adequately protect our business or permit us to maintain our competitive advantage. The following examples are illustrative:

- Others may be able to make compounds that are the same as or similar to our current or future product candidates but that are not covered by the claims of the patents that we own or have exclusively licensed.
- We or any of our licensors or strategic partners might not have been the first to make the inventions covered by the issued patent or pending patent application that we own or have exclusively licensed.
- We or any of our licensors or strategic partners might not have been the first to file patent applications covering certain of our inventions.
- Others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights.
- The prosecution of our pending patent applications may not result in granted patents.
- Granted patents that we own or have exclusively licensed may not provide us with any competitive advantages, or may be held invalid or unenforceable, as a result of legal challenges by our competitors.
- Patent protection on our product candidates may expire before we are able to develop and commercialize the product, or before we are able to recover our investment in the product.
- Our competitors might conduct research and development activities in the U.S. and other countries that provide a safe harbor from patent infringement claims for such activities, as well as in countries in which we do not have patent rights,

and may then use the information learned from such activities to develop competitive products for sale in markets where we intend to market our product candidates.

Roxadustat is considered a Class 2 substance on the 2019 World Anti-Doping Agency Prohibited List which could limit sales and increase security and distribution costs for us and our partners, particularly in China.

Roxadustat is considered a Class 2 substance on the World Anti-Doping Agency ("WADA") Prohibited List. There are enhanced security and distribution procedures we and our collaboration partners and third-party contractors will have to take to limit the risk of loss of product in the supply chain. As a result, our distribution, manufacturing and sales costs for roxadustat, as well as for our partners, will be increased which will reduce profitability. In addition there is a risk of reduced sales due to patient access to this drug. This is particularly the case in China where we will not be able to sell roxadustat in private pharmacies due to the WADA classification. While private pharmacies only represent approximately 10% of the market in China, this will negatively affect sales and therefore the profitability of roxadustat and the Company as a whole.

The existence of counterfeit pharmaceutical products in pharmaceutical markets may compromise our brand and reputation and have a material adverse effect on our business, operations and prospects.

Counterfeit products, including counterfeit pharmaceutical products, are a significant problem, particularly in China. Counterfeit pharmaceuticals are products sold or used for research under the same or similar names, or similar mechanism of action or product class, but which are sold without proper licenses or approvals. Such products may be used for indications or purposes that are not recommended or approved or for which there is no data or inadequate data with regard to safety or efficacy. Such products divert sales from genuine products, often are of lower cost, often are of lower quality (having different ingredients or formulations, for example), and have the potential to damage the reputation for quality and effectiveness of the genuine product. If counterfeit pharmaceuticals illegally sold or used for research result in adverse events or side effects to consumers, we may be associated with any negative publicity resulting from such incidents. Consumers may buy counterfeit pharmaceuticals that are in direct competition with our pharmaceuticals, which could have an adverse impact on our revenues, business and results of operations. In addition, the use of counterfeit products could be used in non-clinical or clinical studies, or could otherwise produce undesirable side effects or adverse events that may be attributed to our products as well, which could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in the delay or denial of regulatory approval by the FDA or other regulatory authorities and potential product liability claims. With respect to China, although the government has recently been increasingly active in policing counterfeit pharmaceuticals, there is not yet an effective counterfeit pharmaceutical regulation control and enforcement system in China. As a result, we may not be able to prevent third parties from selling or purporting to sell our products in China. The proliferation of counterfeit pharmaceuticals has grown in recent years and may continue to grow in the future. The existence of and any increase in the sales and production of counterfeit pharmaceuticals, or the technological capabilities of counterfeiters, could negatively impact our revenues, brand reputation, business and results of operations.

Risks Related to Government Regulation

The regulatory approval process is highly uncertain and we may not obtain regulatory approval for the commercialization of our product candidates.

The time required to obtain approval by the FDA and comparable foreign regulatory authorities is unpredictable, but typically takes many years following the commencement of preclinical studies and clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions. Except in China, We have not obtained regulatory approval for any product candidate, and it is possible that neither roxadustat nor pamrevlumab, nor any future product candidates we may discover, in-license or acquire and seek to develop in the future, will obtain regulatory approval in countries other than China.

Our product candidates could fail to receive regulatory approval from the FDA or other regulatory authorities for many reasons, including:

- disagreement over the design or implementation of our clinical trials;
- failure to demonstrate that a product candidate is safe and effective for its proposed indication;
- failure of clinical trials to meet the level of statistical significance required for approval;
- failure to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;
- disagreement over our interpretation of data from preclinical studies or clinical trials;
- disagreement over whether to accept efficacy results from clinical trial sites outside the U.S. where the standard of care is potentially different from that in the U.S.;

• the insufficiency of data collected from clinical trials of our present or future product candidates to support the submission and filing of an NDA or other submission or to obtain regulatory approval;

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- disapproval of the manufacturing processes or facilities of either our manufacturing plant or third party manufacturers with whom we contract for clinical and commercial supplies; or
- changes in the approval policies or regulations that render our preclinical and clinical data insufficient for approval.

The FDA or other regulatory authorities may require more information, including additional preclinical or clinical data to support approval, which may delay or prevent approval and our commercialization plans, or we may decide to abandon the development program altogether. Even if we do obtain regulatory approval, our product candidates may be approved for fewer or more limited indications than we request, approval may be contingent on the performance of costly post-marketing clinical trials, or approval may require labeling that does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate. In addition, if our product candidates produce undesirable side effects or safety issues, the FDA may require the establishment of REMS or other regulatory authorities may require the establishment of a similar strategy, that may restrict distribution of our approved products, if any, and impose burdensome implementation requirements on us. Any of the foregoing scenarios could materially harm the commercial prospects for our product candidates.

Even if we believe our current or planned clinical trials are successful, regulatory authorities may not agree that our completed clinical trials provide adequate data on safety or efficacy. Approval by one regulatory authority does not ensure approval by any other regulatory authority. However, a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory process in others. We may not be able to file for regulatory approvals and even if we file we may not receive the necessary approvals to commercialize our product candidates in any market.

If our product candidates obtain marketing approval, we will be subject to more extensive healthcare laws, regulation and enforcement and our failure to comply with those laws could have a material adverse effect on our results of operations and financial condition.

If we obtain approval in the U.S. for any of our product candidates, the regulatory requirements applicable to our operations, in particular our sales and marketing efforts, will increase significantly with respect to our operations and the potential for civil and criminal enforcement by the federal government and the states and foreign governments will increase with respect to the conduct of our business. The laws that may affect our operations in the U.S. include:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, to induce, or in return for, the purchase or recommendation of an item or service reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs;
- federal civil and criminal false claims laws and civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third party payors that are false or fraudulent;
- the Health Insurance Portability and Accountability Act of 1996 ("HIPAA"), which created new federal criminal statutes that prohibit executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters;
- HIPAA, as amended by Health Information Technology and Clinical Health Act, and its implementing regulations, which imposes certain requirements relating to the privacy, security, and transmission of individually identifiable health information:
- the federal physician sunshine requirements under the Patient Protection and Affordable Care Act ("PPACA"), which requires manufacturers of drugs, devices, biologics, and medical supplies to report annually to the Centers for Medicare and Medicaid Services ("CMS"), information related to payments and other transfers of value to physicians, other healthcare providers, and teaching hospitals, and ownership and investment interests held by physicians and other healthcare providers and their immediate family members;

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- foreign and state law equivalents of each of the above federal laws, such as the U.S. Foreign Corrupt Practices Act ("FCPA"), anti-kickback and false claims laws that may apply to items or services reimbursed by any third party payor, including commercial insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the applicable compliance guidance promulgated by the federal government, or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways, thus complicating compliance efforts; and
- the Trade Agreements Act ("TAA"), which requires that drugs sold to the U.S. Government must be manufactured in the U.S. or in TAA approved and designated countries. Drugs manufactured in countries not approved under the TAA, may not be sold to the U.S. without specific regulatory approval. We have little experience with this regulation and there is a risk that drugs made from Chinese-made API may not be sold to an entity of the U.S. such as the Veterans Health Administration ("VA") due to our inability to obtain regulatory approval. While there have been recent VA policy changes that appear to allow for sale of drugs from non-TAA approved countries, this policy may change or there may be additional policies or legislation that affect our ability to sell drug to the U.S. Government.

The scope of these laws and our lack of experience in establishing the compliance programs necessary to comply with this complex and evolving regulatory environment increases the risks that we may unknowingly violate the applicable laws and regulations. If our operations are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, the exclusion from participation in federal and state healthcare programs and imprisonment, any of which could materially adversely affect our ability to operate our business and our financial results.

The impact of recent U.S. healthcare reform, its potential partial or full repeal, and other changes in the healthcare industry and in healthcare spending is currently unknown, and may adversely affect our business model.

The commercial potential for our approved products could be affected by changes in healthcare spending and policy in the U.S. and abroad. We operate in a highly regulated industry and new laws, regulations or judicial decisions, or new interpretations of existing laws, regulations or decisions, related to healthcare availability, the method of delivery or payment for healthcare products and services could negatively impact our business, operations and financial condition.

In the U.S., the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 ("MMA") altered Medicare coverage and payments for pharmaceutical products. The legislation expanded Medicare coverage for drug purchases by the elderly and introduced a new reimbursement methodology based on average sales prices for physician-administered drugs. The MMA also provided authority for limiting the number of drugs that will be covered in any therapeutic class and as a result, we expect that there will be additional pressure to reduce costs. For example, the CMS in implementing the MMA has enacted regulations that reduced capitated payments to dialysis providers. These cost reduction initiatives and other provisions of the MMA could decrease the scope of coverage and the price that may be received for any approved dialysis products and could seriously harm our business and financial condition. While the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policies and payment limitations in setting their own reimbursement rates, and any reduction in reimbursement that results from the MMA may cause a similar reduction in payments from private payors. Similar regulations or reimbursement policies have been enacted in many international markets which could similarly impact the commercial potential for our products.

Under the Medicare Improvements for Patients and Providers Act ("MIPPA"), a basic case-mix adjusted composite, or bundled, payment system commenced in January 2011 and transitioned fully by January 2014 to a single reimbursement rate for drugs and all services furnished by renal dialysis centers for Medicare beneficiaries with end-stage renal disease. Specifically, under MIPPA the bundle now covers drugs, services, lab tests and supplies under a single treatment base rate for reimbursement by the CMS based on the average cost per treatment, including the cost of ESAs and IV iron doses, typically without adjustment for usage. It is unknown whether roxadustat, if approved in the U.S., will be included in the payment bundle. Under MIPPA, agents that have no IV equivalent in the bundle are currently expected to be excluded from the bundle until 2025. If roxadustat were included in the bundle, it may reduce the price that could be charged for roxadustat, and therefore potentially limit our profitability. Based on roxadustat's differentiated mechanism of action and therapeutic effects, and discussions with our collaboration partner, we currently believe that roxadustat might not be included in the bundle. If roxadustat is reimbursed outside of the bundle, it may potentially limit or delay market penetration of roxadustat.

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More recently, the PPACA was enacted in 2010 with a goal of reducing the cost of healthcare and substantially changing the way healthcare is financed by both government and private insurers. The PPACA, among other things, increases the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extends the rebate program to individuals enrolled in Medicaid managed care organizations, establishes annual fees and taxes on manufacturers of certain branded prescription drugs, and creates a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D. In addition, other legislative changes have been proposed and adopted in the U.S. since the PPACA was enacted. On August 2, 2011, the Budget Control Act of 2011 created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least \$1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of up to 2% per fiscal year, which went into effect on April 1, 2013.

It is likely that federal and state legislatures within the U.S. and foreign governments will continue to consider changes to existing healthcare legislation. We cannot predict the reform initiatives that may be adopted in the future or whether initiatives that have been adopted will be repealed or modified. The continuing efforts of the government, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce costs of healthcare may adversely affect:

- the demand for any products that may be approved for sale;
- the price and profitability of our products;
- pricing, coverage and reimbursement applicable to our products;
- the ability to successfully position and market any approved product; and
- the taxes applicable to our pharmaceutical product revenues.

Some of the provisions of the PPACA have yet to be fully implemented, while certain provisions have been subject to judicial and Congressional challenges. In January 2017, Congress voted to adopt a budget resolution for fiscal year 2017, that while not a law, is widely viewed as the first step toward the passage of legislation that would repeal certain aspects of the PPACA. Further, on January 20, 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the Affordable Care Act to waive, defer, grant exemptions from, or delay the implementation of any provision of the Affordable Care Act that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. Congress also could consider subsequent legislation to replace elements of the Affordable Care Act that are repealed. Given these possibilities and others we may not anticipate, the full extent to which our business, results of operations and financial condition could be adversely affected by the recent proposed legislation and the Executive Order is uncertain. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our drugs.

Furthermore, legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot be sure whether additional legislative changes will be enacted, or whether FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the regulatory approvals of our product candidates, if any, may be. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent regulatory approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements.

We may not be able to conduct, or contract others to conduct, animal testing in the future, which could harm our research and development activities.

Certain laws and regulations relating to drug development require us to test our product candidates on animals before initiating clinical trials involving humans. Animal testing activities have been the subject of controversy and adverse publicity. Animal rights groups and other organizations and individuals have attempted to stop animal testing activities by pressing for legislation and regulation in these areas and by disrupting these activities through protests and other means. To the extent the activities of these groups are successful, our research and development activities may be interrupted or delayed.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could result in significant liability for us and harm our reputation.

We are exposed to the risk of employee fraud or other misconduct, including intentional failure to:

- comply with FDA regulations or similar regulations of comparable foreign regulatory authorities;
- provide accurate information to the FDA or comparable foreign regulatory authorities;
- comply with manufacturing standards we have established;
- comply with privacy laws protecting personal information;
- comply with federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities;
- comply with the FCPA and other anti-bribery laws;
- report financial information or data accurately;
- or disclose unauthorized activities to us.

Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions, delays in clinical trials, or serious harm to our reputation. We have adopted a code of conduct for our directors, officers and employees, but it is not always possible to identify and deter employee misconduct. The precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could harm our business, results of operations, financial condition and cash flows, including through the imposition of significant fines or other sanctions.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could harm our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations applicable to our operations in the U.S. and foreign countries. These current or future laws and regulations may impair our research, development or manufacturing efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Risks Related to Our International Operations

We are establishing international operations and seeking approval to commercialize our product candidates outside of the U.S., in particular in China, and a number of risks associated with international operations could materially and adversely affect our business.

We expect to be subject to a number of risks related with our international operations, many of which may be beyond our control. These risks include:

- different regulatory requirements for drug approvals in foreign countries;
- different standards of care in various countries that could complicate the evaluation of our product candidates;
- different U.S. and foreign drug import and export rules;

• reduced protection for intellectual property rights in certain countries;

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- changes in tariffs, trade barriers and regulatory requirements;
- different reimbursement systems and different competitive drugs indicated to treat the indications for which our product candidates are being developed;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- compliance with the FCPA, and other anti-corruption and anti-bribery laws;
- U.S. and foreign taxes, including withholding of payroll taxes;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country;
- workforce uncertainty in countries where labor unrest is more common than in the U.S.;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad;
- a reliance on CROs, clinical trial sites, principal investigators and other third parties that may be less experienced with clinical trials or have different methods of performing such clinical trials than we are used to in the U.S.;
- potential liability resulting from development work conducted by foreign distributors; and
- business interruptions resulting from geopolitical actions, including war and terrorism, or natural disasters.

The pharmaceutical industry in China is highly regulated and such regulations are subject to change.

The pharmaceutical industry in China is subject to comprehensive government regulation and supervision, encompassing the approval, registration, manufacturing, packaging, licensing and marketing of new drugs. Refer to "Business — Government Regulation — Regulation in China" for a discussion of the regulatory requirements that are applicable to our current and planned business activities in China. In recent years, the regulatory framework in China regarding the pharmaceutical industry has undergone significant changes, and we expect that it will continue to undergo significant changes. Any such changes or amendments may result in increased compliance costs on our business or cause delays in or prevent the successful development or commercialization of our product candidates in China. For example, the NMPA recently adopted the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines, and accordingly imposed regulatory oversight earlier in our production process for roxadustat manufactured and sold in China. The change in regulatory starting material triggered an extension of the inspection to our contract manufacturer STA, which was successfully completed in October 2018. In addition, Chinese authorities have become increasingly vigilant in enforcing laws in the pharmaceutical industry, in some cases launching industry-wide investigations, oftentimes appearing to focus on foreign companies. The costs and time necessary to respond to an investigation can be material. Any failure by us or our partners to maintain compliance with applicable laws and regulations or obtain and maintain required licenses and permits may result in the suspension or termination of our business activities in China.

We plan to use our own manufacturing facilities in China to produce roxadustat API, roxadustat drug product, and FG-5200 corneal implants. As an organization, we have limited experience in the construction, licensure, and operation of a manufacturing plant, and accordingly we cannot assure you we will be able to meet regulatory requirements to operate our plant and to sell our products.

We have two manufacturing facilities in China, with one located in Beijing and the other in Cangzhou, Hebei. In December 2018, we received the Manufacturing License for Drug Substance and Drug Product for roxadustat and GMP certification for our Beijing facility that allows us to manufacture limited commercial quantities of roxadustat capsules. We are currently planning on manufacturing commercial-scale API at our Cangzhou facility, and expect to receive a license to produce roxadustat API at that site in the second half of 2019. However, as an organization, we have limited experience licensing and operating commercial manufacturing facilities.

We will be obligated to comply with continuing cGMP requirements and there can be no assurance that we will receive and maintain all of the appropriate licenses required to manufacture our product candidates for clinical and commercial use in China. In addition, we and our product suppliers must continually spend time, money and effort in production, record-keeping and quality assurance and appropriate controls in order to ensure that any products manufactured in our facilities meet applicable specifications and other requirements for product safety, efficacy and quality and there can be no assurance that our efforts will succeed for licensure or continue to be successful in meeting these requirements.

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We would require separate approval for the manufacture of FG-5200. In addition, we may convert the existing manufacturing process of FG-5200 to a semi-automated process, which may require us to show that implants from our new manufacturing process are comparable to the implants from our existing manufacturing process. There can be no assurance that we will successfully receive licensure and maintain approval for the manufacture of FG-5200, either of which would be expected to delay or preclude our ability to develop FG-5200 in China and may materially adversely affect our business and operations and prospects in China.

Manufacturing facilities in China are subject to periodic unannounced inspections by the NMPA and other regulatory authorities. We expect to depend on these facilities for our product candidates and business operations in China. Natural disasters or other unanticipated catastrophic events, including power interruptions, water shortages, storms, fires, earthquakes, terrorist attacks, government appropriation of our facilities, and wars, could significantly impair our ability to operate our manufacturing facilities. Certain equipment, records and other materials located in these facilities would be difficult to replace or would require substantial replacement lead time that would impact our ability to successfully commercialize our product candidates in China. The occurrence of any such event could materially and adversely affect our business, financial condition, results of operations, cash flows and prospects.

In addition to manufacturing, we are responsible for pharmacovigilance, medical affairs, and management of the third party distribution logistics for roxadustat in China. We have no experience in these areas as a company, and accordingly we cannot assure you we will be able to meet regulatory requirements or operate in these capacities successfully.

We are responsible for commercial manufacturing, pharmacovigilance, medical affairs, and management of the third party distribution logistics for roxadustat commercial activities in China. While we have been increasing our staffing in these areas, as a company, we have no experience managing or operating these functions for a commercial product and there can be no guarantee that we will do so efficiently or effectively. Mistakes or delays in these areas could limit our ability to successfully commercialize roxadustat in China, could limit our eventual market penetration, sales and profitability, and could subject us to significant liability in China.

Our decision to launch roxadustat in China prior to approval in the U.S. or Europe is largely unprecedented and could be subject to significant risk, delay and expense.*

Even though our subsidiary FibroGen Beijing has received marketing authorization for roxadustat for anemia caused by CKD in dialysis patients, we have not yet received approval in non-dialysis patients, and are awaiting the results from the Chinese authorities' completed inspection of our Phase 3 non-dialysis clinical trial sites.

We are currently expecting non-dialysis patients to be added to our approved dialysis label for roxadustat in China in mid-2019, and are planning on launching in the third quarter of 2019, however, it is possible that unforeseen delays in the China regulatory process could have a material adverse effect on our development and commercialization of roxadustat in China.

In addition we will be required to conduct a 2,000 subject post-approval safety study to demonstrate the long-term safety of roxadustat, as well as provide period reporting to the authorities on GMP and quality compliance at our manufacturing facilities. If safety issues arise in this study, or generally after commercialization, our commercialization plans and profitability in China could be negatively impacted.

We and our collaboration partner in China, AstraZeneca, may experience difficulties in successfully generating sales of roxadustat in China.

We and AstraZeneca have a profit sharing arrangement with respect to roxadustat in China and any difficulties we may experience in generating sales will affect our bottom line. Difficulties may be related to our ability to obtain reasonable pricing, reimbursement, hospital listing, and tendering, or other difficulties related to distribution, marketing, and sales efforts in China. Sales of roxadustat in China may be limited due to the complex nature of the healthcare system, low average personal income, pricing controls, still developing infrastructure and potentially rapid competition from other products. The government has committed to updating the National Reimbursement Drug List ("NRDL") in 2019. Previous updates to the NRDL occurred in 2017 and 2009. In addition, there were also NRDL price negotiations in 2018 for oncology drugs. Admission to the NRDL depends on a number of factors, including onmarket experience, scale of patient adoption, physician endorsement, cost effectiveness and budget impact. Given that roxadustat was approved at the end of 2018, we may or may not qualify for the NRDL update in 2019. In particular, if we are unable to obtain reimbursement for roxadustat through the 2019 update to the NRDL, we may have to wait a substantial period of time before the reimbursement drug list is updated again. Without government reimbursement, many patients will not be able to afford roxadustat, since private commercial health insurance is rare, and our business and operations could be adversely affected. Therefore reimbursement and obtaining hospital listing is critical to roxadustat's near-term commercial success in China.

The market for treatment of anemia in CKD in China is highly competitive.

Although we have now received approval for roxadustat for the treatment of anemia caused by CKD in dialysis patients in China, and even if roxadustat receives approval for anemia caused by CKD in non-dialysis patients, it faces intense competition in the market for treatment of anemia in CKD. Roxadustat would compete with ESAs, which are offered by established multinational pharmaceutical companies such as Kyowa Hakko Kirin China Pharmaceutical Co., Ltd., Roche and Chinese pharmaceutical companies such as 3SBio Inc. and Di'ao Group Chengdu Diao Jiuhong Pharmaceutical Factory. Many of these competitors have substantially greater name recognition, scientific, financial, and marketing resources, as well as established distribution capabilities. Many of our competitors have more resources to develop or acquire, and more experience in developing or acquiring, new products and in creating market awareness for those products. Many of these competitors have significantly more experience than we have in navigating the Chinese regulatory framework regarding the development, manufacturing and marketing of drugs in China, as well as in marketing and selling anemia products in China. Additionally, we believe that most patients with anemia in CKD in China are currently being treated with traditional Chinese medicine, which is widely accepted and highly prevalent in China. Traditional Chinese medicine treatments are often oral and thus convenient and low-cost, and practitioners of traditional Chinese medicine are numerous and accessible in China. As a result, it may be difficult to persuade patients with anemia in CKD to switch from traditional Chinese medicine to roxadustat.

The Chinese government is implementing a new "Two Invoices" regulation which could affect the way we structure our distributorship relationships in China for roxadustat.

The Chinese government is implementing new regulations that impact distribution of pharmaceutical products in China. These regulations generally require that at most two invoices may be issued throughout the distribution chain. Failure to comply with the "Two-Invoices" regulations would prevent us from accessing the market in China. We are planning on modifying the distribution responsibilities under the China Agreement between AstraZeneca and FibroGen such that FibroGen would engage distributors and a third party logistics provider, and both companies will work together to manage the distribution network. FibroGen China has never managed distribution of pharmaceutical products, and this new distribution structure may impose higher costs or limit or delay our ability to sell products to our principal customers, and may limit the near term sales of our products.

There is no assurance that roxadustat will be included in the Medical Insurance Catalogs.

Eligible participants in the national basic medical insurance program in China, which consists of mostly urban residents, are entitled to reimbursement from the social medical insurance fund for up to the entire cost of medicines that are included in the Medical Insurance Catalogs. Refer to "Business — Government Regulation — Regulation in China." We believe that the inclusion of a drug in the Medical Insurance Catalogs can substantially improve the sales of a drug in China. The Ministry of Labor and Social Security in China ("MLSS") together with other government authorities, select medicines to be included in the Medical Insurance Catalogs based on a variety of factors, including treatment requirements, frequency of use, effectiveness and price. The MLSS also occasionally removes medicines from such catalogs. There can be no assurance that roxadustat will be included, and once included, remain in the Medical Insurance Catalogs. The exclusion or removal of roxadustat from the Medical Insurance Catalogs may materially and adversely affect sales of roxadustat.

Even if FG-5200 can be manufactured successfully and achieve regulatory approval, we may not achieve commercial success.

We have not yet received a license to manufacture FG-5200 in our Beijing manufacturing facility or at scale, and we will have to show that FG-5200 produced in our China manufacturing facility meets the applicable regulatory requirements. There can be no assurance that we can meet these requirements or that FG-5200 can be approved for development, manufacture and sale in China.

Even if we are able to manufacture and develop FG-5200 as a medical device in China, the size and length of any potential clinical trials required for approval are uncertain and we are unable to predict the time and investment required to obtain regulatory approval. Moreover, even if FG-5200 can be successfully developed for approval in China, our product candidate would require extensive training and investment in assisting physicians in the use of FG-5200.

The retail prices of any product candidates that we develop may be subject to control, including periodic downward adjustment, by Chinese government authorities.

The price for pharmaceutical products is highly regulated in China, both at the national and provincial level. Price controls may reduce prices to levels significantly below those that would prevail in less regulated markets, or limit the volume of products that may be sold, either of which may have a material and adverse effect on potential revenues from sales of roxadustat in China. Moreover, the process and timing for the implementation of price restrictions is unpredictable, which may cause potential revenues from the sales of roxadustat to fluctuate from period to period.